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Defective regulated secretion: A trigger for Alzheimer's pathology?

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ABSTRACT

Extracellular amyloid plaques formed from aggregated Amyloid-β (Aβ), a specific cleavage product of Amyloid Precursor Protein (APP), and intracellular tau-containing neurofibrillary tangles are the two key histopathological hallmarks of Alzheimer's Disease (AD). However, increasing evidence suggests that the trigger for neurodegeneration in AD involves intraneuronal defects in endolysosomes, which might be induced by both Aβ and tau. Recent high-resolution analysis of trafficking inside neuronal and non-neuronal cells suggests such defects may arise through aberrant compartmental maturation events during regulated secretion. These events bring together APP, secretory and endosomal compartments, and also the proteolytic secretases that generate Aβ. They may be initiated by the accumulation of Aβ and/or C-terminal fragments of APP, which interfere with endolysosomal trafficking and potentially induce tau pathology. They also lead to secretion of proteins from these Aβ-containing compartments, which can trigger endolysosomal phenotypes in other cells that endocytose them. By implicating regulated secretion in the initiation of AD, this new model highlights novel intracellular mechanisms that might drive neurodegeneration. Identifying suppressors of these pathways could suggest entry points for the development of novel therapies that target the earliest stages of AD pathology.

1. Introduction

As lifespan continues to increase, Alzheimer's Disease (AD), the most common form of dementia, is becoming increasingly prevalent worldwide (Gustavsson et al., 2023). Although some rare forms of AD are familial, most AD patients suffer from a sporadic form of the disease linked to genetic and environmental risk factors. AD is associated with two histopathological hallmarks: intracellular neurofibrillary tangles assembled from hyperphosphorylated cytoskeletal tau protein (Rawat et al., 2022) and extracellular amyloid plaques containing Amyloid-β (Aβ) peptides generated through cleavage of the transmembrane Amyloid Precursor Protein (APP) by β- and γ-secretases (Weglinski and Jeans, 2023) (Fig. 1). APP can be processed by two different proteolytic pathways, non-amyloidogenic and amyloidogenic. Initiation of the non-amyloidogenic route, which primarily takes place at the plasma membrane, involves cleavage by α-secretase at a site within the Aβ sequence, thus preventing the generation of Aβ (Fig. 1). In the amyloidogenic pathway, sequential cleavage by β-secretase and then γ-secretase produces Aβ. Aβ is normally produced at low levels in neurons, where it has been proposed to undertake multiple roles, including regulation of synaptic activity, sealing leaks in the blood-brain barrier and anti-microbial functions (Brothers et al., 2018). The β-secretase--cleaved transmembrane APP C-terminal fragment that has not been cut by γ-secretase (APP-βCTF or C99), is also reported to disrupt endolysosomal trafficking and be neurotoxic (Vrancx and Annaert, 2025).

Mutant *APP* alleles that encode amyloidogenesis-prone forms of Aβ or promote increased β-secretase cleavage are associated with rare cases of familial AD (Wang et al., 2024), strongly implicating aggregation of Aβ as a disease trigger and supporting the long-standing 'amyloid hypothesis' (Selkoe and Hardy, 2016). However, recently developed

Abbreviations: Aβ, β-amyloid peptide; AD, Alzheimer's Disease; ALS, amyotrophic lateral sclerosis; ApoE, Apolipoprotein E; APP, Amyloid Precursor Protein; APP-CTF, APP C-terminal fragment; APPL, APP-like *Drosophila* APP; ARC, activity-regulated cytoskeleton-associated protein; BACE1, Beta-site Amyloid Precursor Protein Cleaving Enzyme 1; DCG, dense-core granule; ESCRT, Endosomal Sorting Complexes Required for Transport; EV, extracellular vesicle; ILV, intraluminal vesicle; LEL, late endosomes and lysosomes; MVB, multivesicular body; PMEL, premelanosome protein; PSEN2, Presenilin-2 γ-secretase; TGN, *trans*-Golgi network.

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anti-amyloid antibodies that target plaques appear to have modest inhibitory effects on disease progression in only a subset of patients (Kim et al., 2025). Indeed, amyloid plaques are not always associated with dementia, while cognitive decline can initiate long before plaques are detected (Morris et al., 2014). These findings are more consistent with a refined amyloid hypothesis in which aggregated Aβ-oligomers, Aβ-fibrils and/or other APP-derived catabolites residing outside plaques are the central players, which trigger neurodegeneration.

One appealing model that has emerged postulates that Aβ-induced defects in trafficking of neuronal endolysosomal compartments (marked 'X' in Fig. 2) lead to degeneration (Cataldo et al., 1996; Kimura and Yanagisawa, 2018). Indeed, endolysosomal trafficking regulators are commonly identified as AD susceptibility genes in genome-wide association screens (GWAS) (Ando et al., 2021), and their contribution to genetic risk appears to correlate with neuronal pathology (Mamde et al., 2025).

In an extension of this 'traffic jam' model (Kimura and Yanagisawa, 2018), in sporadic disease, endolysosomal defects might be triggered or exacerbated by neurofibrillary tangles, metabolic stress and by combinations of genetic and environmental factors, which may also involve glial and/or inflammatory pathologies (Roda et al., 2022; Deng et al., 2024) (Fig. 2B). Analysing the fate of APP and Aβ as they traffic through cells could help to identify how and where these endolysosomal defects evolve. Until recently, however, such studies suggested disparate functions for multiple intracellular compartments, which were difficult to integrate into a unified model.

2. Aβ formation: roles for secretory and endolysosomal systems

Like other highly secretory cells, neurons require trafficking pathways that release proteins and other macromolecules into the extracellular space, and also retrieve extracellular and membrane-associated molecules at the plasma membrane (Alberts et al., 2002). Intracellular trafficking routes that deliver proteins to the cell surface include the constitutive and regulated secretory pathways: regulated secretory compartments form at the *trans*-Golgi network (TGN) and release signalling molecules, such as neuropeptides, typically in response to increased intracellular calcium ion concentration (route marked '1' in Fig. 3A). There is strong evidence that neuropeptides have fundamental roles in brain development, as well as remodelling and maintenance of synapses, and that their synaptic release is frequently activity-dependent (Nusbaum et al., 2017; Guillaumin and Burdakov, 2021; Hevesi et al., 2025).

The endolysosomal system consists of a degradation pathway, involving late endosomes and lysosomes (LELs), and several recycling endosomal routes ('2' and '3' respectively in Fig. 3A). These can be distinguished because the recycling compartments are labelled with different Rab GTPases, a large family of monomeric G proteins that regulate compartmental identity and intercompartmental vesicular trafficking (Stenmark, 2009; Wilmes, Kümmel, 2023). In neurons, non-peptide neurotransmitters are concentrated into specialised recycling endosomes in preparation for activity-dependent synaptic secretion (Ivanova and Cousin, 2022), operating in parallel with neuropeptide-containing regulated secretory compartments. Secretory and endosomal compartments can directly exchange cargos with each other via vesicular transport or indirectly through the Golgi apparatus and plasma membrane. For example, secretory vesicles in the constitutive pathway can be trafficked from the TGN to nearby endosomes carrying the slow recycling endosomal marker Rab11 (Welz et al., 2014; Nakano, 2022; '5' in Fig. 3A), while recycling endosomes are also involved in retrograde transport back to the TGN (Maxfield and McGraw, 2004; Vale-Costa and Amorim, 2016; '4' in Fig. 3A). However, until recently, it was thought that regulated secretory and endosomal compartments do not usually coalesce (Fig. 3A).

In neurons, how is APP trafficked through these compartments and where does it encounter β-secretase, known as BACE1, to initiate the

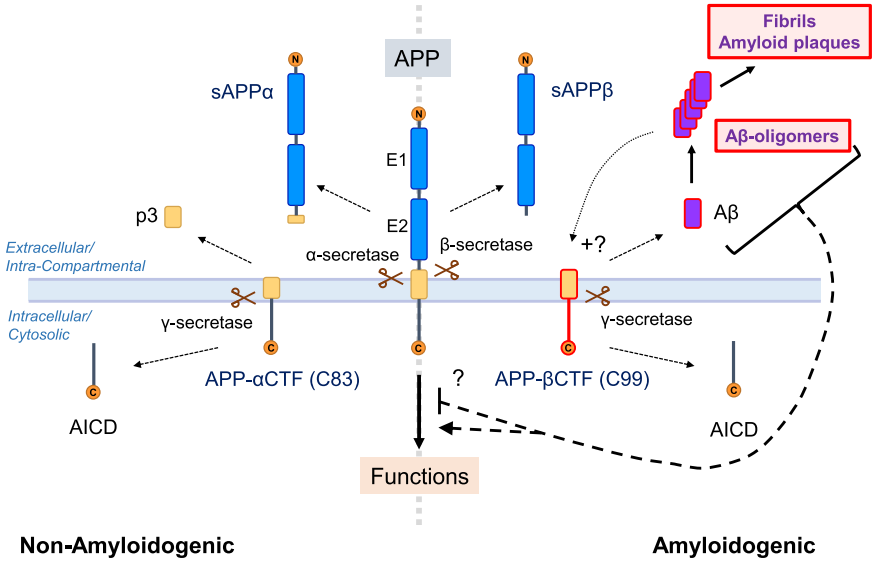

Fig. 1. Non-Amyloidogenic and Amyloidogenic Processing of APP. Schematic summarises the two APP processing events that generate non-amyloidogenic and amyloidogenic peptides. APP is a transmembrane protein containing two conserved extracellular domains (E1 and E2), a transmembrane domain and an intracellular C-terminal domain with some evolutionarily conserved functions from humans to flies. In the non-amyloidogenic pathway, cleavage by α-secretase releases the APP extracellular domain (secreted amyloid precursor protein α; sAPPα). Subsequent γ-secretase cleavage generates a non-amyloidogenic peptide, p3, releasing the APP intracellular domain (AICD) from the membrane. In the amyloidogenic pathway, sequential cleavage by β-secretase and then γ-secretase produces the AICD and amyloidogenic Aβ-peptides of different lengths, including Aβ43, Aβ42 and Aβ40. These peptides, particularly Aβ42, are prone to aggregation, forming neurotoxic oligomers and fibrils, both inside and outside cells, which can cluster to produce extracellular amyloid plaques. Aβ42 and its oligomerised forms can also promote or interfere with specific APP functions (see Section 5). In addition, transmembrane APP C-terminal fragments (APP-CTF) that have not been cut by γ-secretase, particularly the product of β-secretase cleavage (C99), are reported to be neurotoxic. Full-length APP has biological functions, including roles in DCG compartment maturation and membrane-dependent protein aggregation, and some of these functions are reported to be modulated by Aβ and/or Aβ-oligomers. Neurotoxic components of the amyloidogenic pathway are outlined in red.

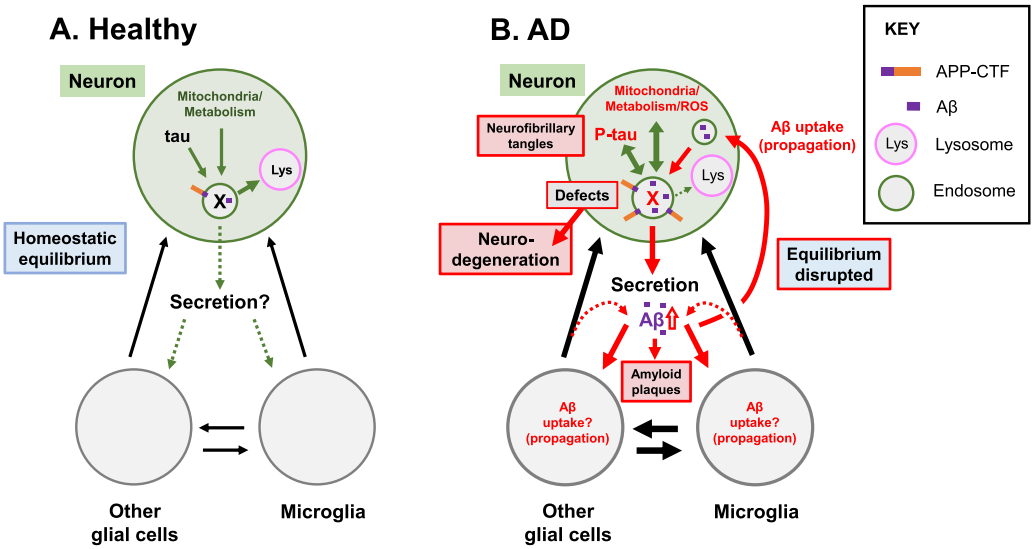

Fig. 2. Generation of AD Pathology Associated With Stalled Late Endosomal Compartments. Schematics compare late endosomes in neurons from healthy individuals with those in AD patients, where lysosomal trafficking is blocked, producing an endolysosomal 'traffic jam'; the inputs that might trigger or exacerbate this blockade are highlighted in red text in B. The different subcellular regions within neurons, such as synaptic and dendritic domains, are not distinguished in these schematics, although the key pathological interactions shown are thought to most likely initiate at the synapse. In the endolysosomal 'traffic jam' model, initiation of neurodegenerative events involves trafficking defects in late endosomal compartments, which contain Aβ and potentially pathological APP-C-terminal fragments (APP-CTFs), particularly APP-βCTF. These compartments may be present and homeostatically regulated in healthy cells (marked with black 'X'; **A**). They are involved in APP processing and Aβ formation with the resulting molecules normally being trafficked to lysosomes (Lys) for degradation. In AD, these late endosomal compartments (red 'X'; **B**) accumulate Aβ and APP-CTFs, fail to be fully degraded by lysosomes and build up preferentially in presynaptic terminals. In sporadic AD, the most expansive version of this model posits that this endolysosomal trafficking defect can be induced by Aβ, APP-CTFs, phosphorylated tau, metabolic stress, interneuronal propagation, and altered signalling by other cell types that normally maintain homeostatic equilibrium in the brain. The resulting pathology may be exacerbated by multiple positive feedback loops, progressively leading to characteristic AD hallmarks (red boxes).

multi-step process of Aβ formation? In healthy neurons of humans and other mammals expressing endogenous levels of APP and BACE1, there are only low levels of overlap between these two proteins; high-resolution and super-resolution microscopy studies of exogenous fluorescent APP and BACE1 also suggest limited co-localisation, which in response to synaptic activity, is increased in recycling endosomes (Das et al., 2013; Wang et al., 2024).

Studies focused on AD-associated defects in compartment and vesicle trafficking, or on pathological APP processing in sporadic and familial AD have suggested both secretory and endosomal pathways are involved. For example, an analysis in human HeLa cancer cells and rat primary neurons indicated that clathrin adaptor AP-1, which controls maturation of regulated secretory compartments, is essential for release of APP from the Golgi and its pathological processing (Januário et al., 2022). However, endosomes marked by the slow recycling endosomal marker Rab11 are reported to be the major compartments in which APP and β-secretase BACE1 interact (Buggia-Prévot et al., 2014; Das et al., 2016) (Fig. 3A). Furthermore, in both human and rodent models, extracellular Aβ-oligomers can modulate APP's signalling functions, inducing further Aβ generation, at least some of which accumulates in recycling endosomes (Rolland et al., 2020; Antonino et al., 2022). Synaptic activity not only increases colocalization of APP and BACE1 in recycling endosomes (Wang et al., 2024), it is also thought to play a key role in propagation of pathological Aβ-oligomers (Tampellini and Gouras, 2010). However, in the conventional model of secretory trafficking, this activity promotes release of neuropeptides and small-molecule neurotransmitters from regulated secretory and recycling endosomal compartments respectively.

Other studies have highlighted the importance of LELs in intracellular Aβ production (Fig. 3A); Presenilin-2 (PSEN2), the exclusively intracellular γ-secretase that generates Aβ (Fig. 1), primarily resides in these compartments (Ni et al., 2006; Sannerud et al., 2016; Strooper and Annaert, 2016). Indeed, prior to amyloid plaque formation, in a mouse model of AD, Aβ-fibrils are reported to form in synaptic multivesicular bodies (MVBs) (Eckman et al., 2023), which have historically been equated to late endosomes. The intraluminal vesicles (ILVs) inside MVBs are secreted as exosomes when these compartments fuse with the plasma membrane (Fig. 3A) (Dixson et al., 2023). Evidence, using rodent models and human cells, is increasing that secreted Aβ-oligomers and amyloid plaques are associated with exosomes and/or other extracellular vesicles (EVs), and these vesicles affect the distribution and pathological effects of Aβ-oligomers (eg. Rajendran et al., 2006; Dinkins et al., 2016; Sardar Sinha et al., 2018; Mowry et al., 2023).

Ultimately, Aβ has been shown to accumulate in many different compartments within AD neurons, including the ER, Golgi/TGN, a range of endosomes and lysosomes (Wang et al., 2024), though for some compartments, it may be trafficked there from the key compartments involved in Aβ generation, especially in the early stages of pathology. Nevertheless, both secretory and endosomal compartments appear to be involved in generating Aβ and driving pathology, raising the question of how APP sequentially reaches these compartments,

One conventional explanation is that co-ordinated secretion/endocytosis and/or vesicular trafficking shuttles APP and its derivatives between compartments either via the plasma membrane or intracellularly, and these events become mis-regulated in a reproducible way in AD. For example, Golgi fragmentation is a commonly observed defect in the cell bodies of neurons in several neurodegenerative diseases, including AD (Fourriere and Gleeson, 2026). It is also one of the earliest organelle phenotypes in human induced pluripotent stem cell (iPSC) neuronal models of AD (Haukedal et al., 2023). Such fragmentation can lead to disruption of the normally separated anterograde trafficking of APP and BACE1 through the Golgi apparatus (Tan et al., 2020), thus permitting generation of pathological Aβ and APP-βCTF in this location (Fourriere and Gleeson, 2026).

A more radical alternative explanation to defective shuttling of APP and BACE1 generating pathology is that entire secretory compartments switch to endosomal identities through compartmental fusion during normal maturation and quality control steps, and that these transition

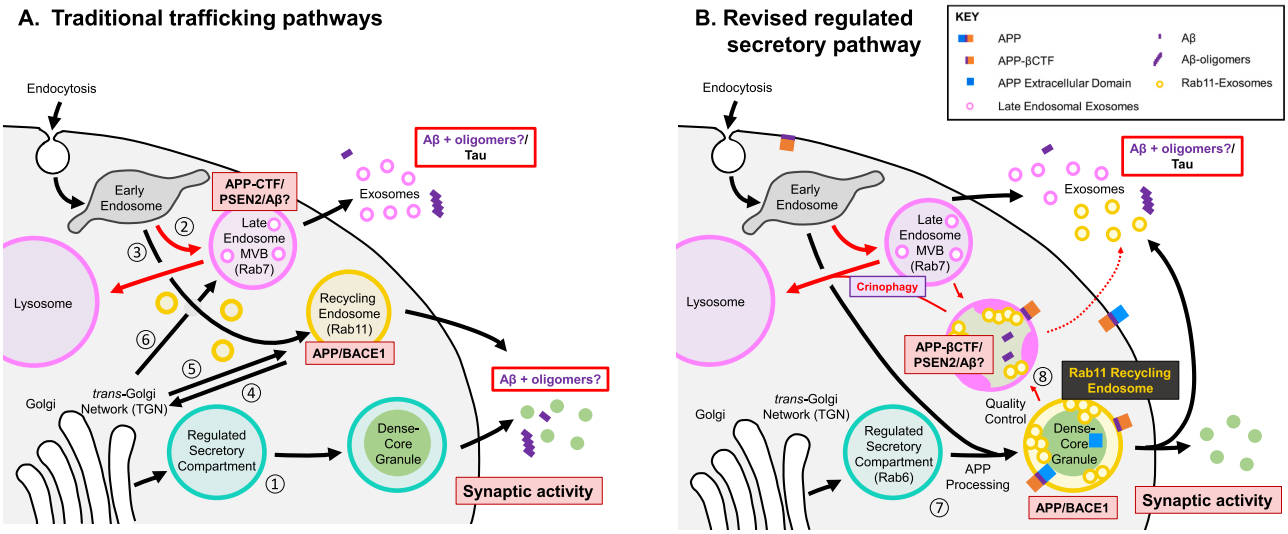

Fig. 3. AD-Relevant Events in the Regulated Secretory and Endosomal Trafficking Pathways: Conventional and Revised Models. A. Schematic shows the conventional model for regulated secretion and endosomal trafficking, and highlights multiple compartments associated with APP processing and Aβ-oligomer secretion. In contrast to the constitutive secretory pathway (not shown), regulated secretory compartments (marked '1') mature by aggregating proteins destined for secretion into dense-core granules that are only released and dissipated when the cell is stimulated, typically mediated via an intracellular Ca^{2+} signal. Late endosomes form multivesicular bodies by inward budding of the limiting membrane and the resulting intraluminal vesicles (ILVs) can be released as exosomes if the compartment fuses with the plasma membrane rather than the lysosome (route '2'). There are multiple fast and slow recycling endosomal pathways with small GTPase Rab11 controlling a major slow recycling route (route '3'). All pathways appear to play a role in Aβ generation and secretion. Most notably, APP and BACE1 primarily encounter each other in recycling endosomes, and APP-CTFs are most likely cleaved by γ-secretase in the LEL pathway. Proteins in specific compartments can traffic to other compartments via vesicular transport, eg. Rab11-positive recycling endosomes to TGN (route '4'), TGN to recycling endosomes (route '5'), TGN to late endosomes (route '6'), etc. **B.** Revised model of regulated secretion in which DCG compartment maturation requires a Rab11-recycling endosomal input that also induces ILV biogenesis (marked '7'). Normal quality control mechanisms can target defunct compartments for lysosomal degradation via several related processes that are collectively termed 'crinophagy', which requires interactions with LEL and autophagic compartments (route '8'). Therefore, regulated secretory compartments can progress to recycling and then late endosomal identity, as they mature and pass through the quality control system. In this model, full-length APP, which could reach DCG compartments either through the regulated secretory pathway or via recycling endosomes, can be cleaved by β-secretase BACE1, when they meet inside maturing DCG compartments and then by γ-secretase PSEN2 in the degradative quality control pathway (APP trafficking and processing shown schematically; mechanisms discussed in more detail for secondary cells in Section 4 and Fig. 4). Any secretion from the intermediate compartments generated in this pathway as a result of endolysosomal trafficking defects (dotted arrow) could release Aβ, Aβ-oligomers and exosomes, and potentially propagate pathology to other neurons. Note that these defects may also be associated with accumulation and (exosome-associated) secretion of APP-βCTF, which is independently implicated in the induction of AD-related phenotypes (see Sections 4 and 7; Fig. 4B).

processes malfunction in AD (Fig. 3B).

3. Endosomal contributions to regulated secretion

Regulated secretory compartments form at the *trans*-Golgi network, but they then must mature, a process involving the aggregation of soluble proteins within them into a central insoluble dense-core granule (DCG), prior to compartmental fusion with the plasma membrane and dissipation of the contents (Fig. 3A; Gondré-Lewis et al., 2012). During maturation, these compartments undergo quality control steps, which are poorly defined, but can lead to some defunct secretory compartments being recycled via various autophagy-related mechanisms (Szenci et al., 2023). These degradative processes are frequently referred to as crinophagy. They can either be mediated by direct fusion with lysosomes, or following intermediate steps, with the machinery involved sharing similarities with late endosomal/lysosomal heterotypic fusion or late endosomal homotypic fusion (Zhou et al., 2020; Li et al., 2022; Boda et al., 2023).

Characterisation of the accompanying transitions in compartmental identity during these maturation and quality control processes requires robust markers for each compartment and real-time imaging. However, most secretory and endosomal compartments are smaller than the wavelength of light (<250 nm diameter), and so electron microscopic or super-resolution techniques are required to distinguish them from neighbouring compartments. Only the latter method employs living cells.

An alternative approach is to use cells with enlarged compartments. Secondary cells, prostate-like secretory cells of the male accessory gland in the fruit fly, *Drosophila melanogaster*, have about ten giant secretory compartments of approximately 5 μm in diameter (Redhai et al., 2016; Wells et al., 2023). Like other secretory cells, these compartments package their soluble proteins into a DCG; this process is controlled by established DCG compartment regulators, like Arf1 and AP-1, and can be followed in real time *ex vivo* in cultured glands (Wells et al., 2023). Importantly, these compartments form at the TGN and are labelled by the TGN and post-Golgi marker Rab6, but they then receive recycling endosomal inputs and gradually transition to Rab11 identity, a change required for DCG formation (Wells et al., 2023) (marked '7' in Fig. 3B).

Rab11 also coats specific compartments leaving the TGN in yeast (Thomas et al., 2021) and is a marker for more mature DCG compartments in several *Drosophila* and mammalian cell types (eg. Neuman et al., 2021; Sugawara et al., 2009), including *Drosophila* (Beronja et al., 2005) and rat (Khvotchev et al., 2003) neurons. In mammals, there are two forms of Rab11, Rab11a and Rab11b, both of which may be involved in this process (Khvotchev et al., 2003). Super-resolution studies in human HeLa cervical cancer cells reveal that Arf1-positive secretory compartments transition to Rab11a identity after they leave the TGN (Stockhammer et al., 2024), suggesting that the maturation event observed in *Drosophila* secondary cells is highly evolutionarily conserved. Indeed, *Rab6* deletion also blocks maturation of synaptic vesicles in mammalian neurons (Zhang et al., 2024), and Rab11 plays a major role in presynaptic function in flies and mammals (Kang et al., 2024; Kokotos et al., 2018), consistent with the Rab6 to Rab11 transition mechanism being employed in synaptic secretion.

The Rab11-positive DCG compartments in secondary cells also contain ILVs, which are secreted as a specific subtype of exosomes called Rab11-exosomes, also produced in human cancer cells under the control of Rab11a (Fan et al., 2020). Like DCG formation, Rab11-exosome biogenesis is dependent on the Rab11 compartmental transition (Wells et al., 2023). Interestingly, recent electron microscopic analysis using cryo-fixation of bovine adrenal chromaffin neuron-like cells suggests that mammalian DCG compartments can also contain ILVs (Wang et al., 2025), contrasting with many previous studies that employed alternative fixation methods. Furthermore, Koles et al. (2012) have demonstrated in *Drosophila* that Evenness Interrupted (Evi), a co-secreted binding protein for the Wnt family signalling molecule Wingless, is released in a Rab11-dependent fashion from presynaptic termini at the larval neuromuscular junction on exosomes formed in MVBs. Therefore, exosome biogenesis may be much more frequently associated with the regulated secretory pathway than has previously been thought

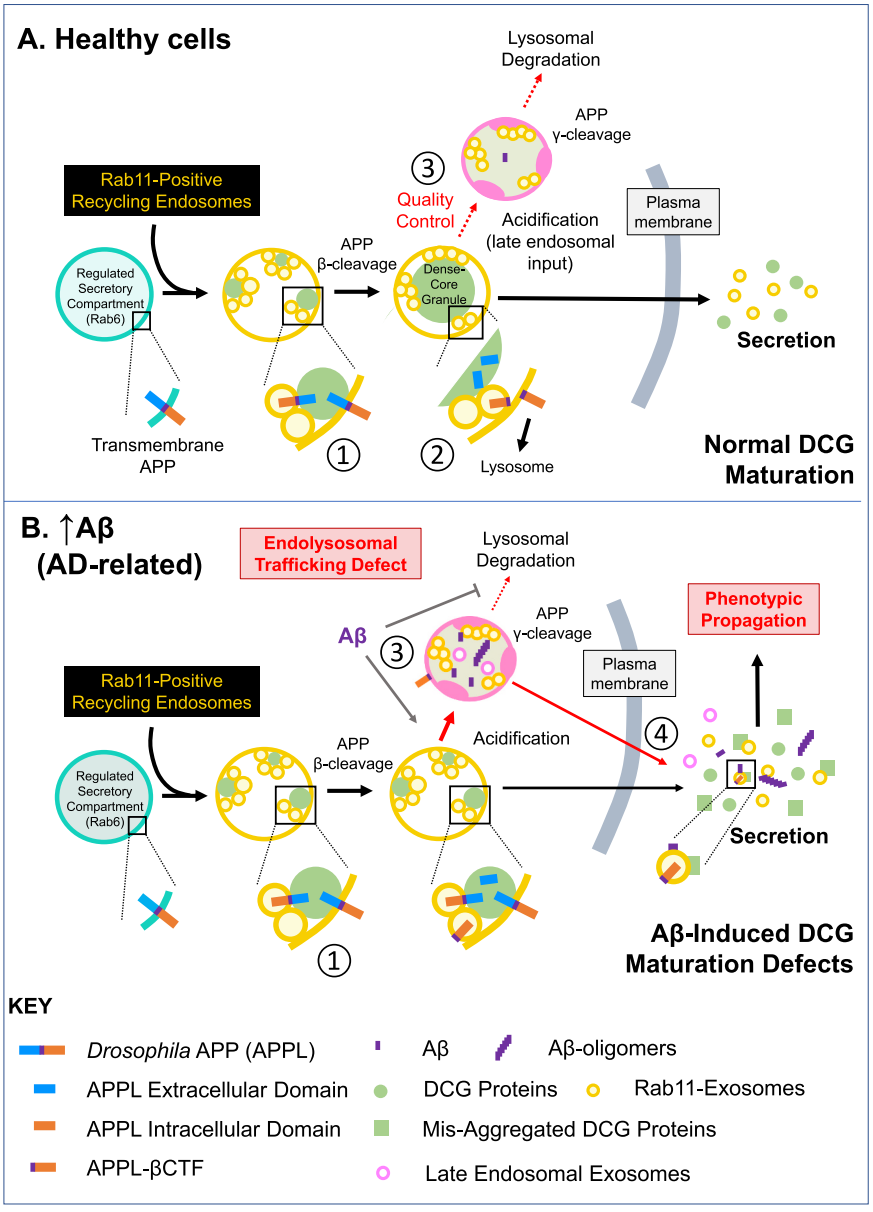

Fig. 4. APPL and Aβ in Regulated Secretion. Model, developed from studies in *Drosophila*, summarises how fly APP (APPL) is processed (shown in magnified insets) during normal DCG compartment maturation in secondary cells (**A**) and how this process is disrupted in the presence of accumulated Aβ, leading to endolysosomal trafficking defects that can propagate to other cells (**B**). Importantly, APPL's functions in controlling DCG aggregation can be replaced by human APP. **A.** Membrane-associated APPL plays a key role in regulating normal aggregation of DCG proteins (step '1') and must then be cleaved, probably at the β-secretase site, during further maturation of DCG compartments to separate aggregates from membranes (step '2'). Typically, only a small proportion of DCG compartments are targeted to lysosomes and degraded through quality control processes that will lead to limited Aβ production through γ-secretase cleavage (step '3'). As discussed in the text (Sections 5 and 6), based on a range of studies in mammalian and fly systems, we hypothesise that other molecules with links to AD and neurodegeneration are also involved in DCG compartment maturation and, as in the case of Aβ (**B**), their misregulation may induce endolysosomal trafficking defects that initiate or exacerbate AD pathology. **B.** When Aβ over-accumulates in cells, DCG compartment maturation is affected and some APPL is not properly processed. Aberrant acidified DCG compartments, potentially containing Aβ and APP-βCTF, fail to traffic normally to lysosomes for degradation in the quality control pathway, mirroring an early defect in AD (step '3'; red box). Some of these compartments appear to secrete their contents, including exosomes containing APP proteolytic fragments and carrying extracellular Aβ and protein aggregates (step '4'). These contents can induce endolysosomal defects in other cells that endocytose them, as is also observed in AD (second red box). Since amyloidogenic mutant Aβ peptides can have more severe effects on DCG biogenesis and intercellular phenotypic propagation, it is likely that oligomerised forms of Aβ are involved in these defects.

(Goberdhan et al., 2026), including in neurons.

The discovery that regulated secretion is intimately linked to the recycling endosomal system provides a route by which LELs might also input through crinophagy. In the case of secondary cells, there appears to be a partial acidification process first, potentially preceded by late endosome-associated Rab7 recruitment to DCG compartments, and followed by fusion to this cell's large lysosomes ('8' in Fig. 3B; Fan et al., 2020; Singh et al., 2025). In mammalian neurons, autophagy-related processes play key roles in recycling presynaptic secretory compartments (Mishra et al., 2024), and trafficking of lysosomes to presynaptic termini is required for clearance of those compartments targeted for degradation (Farfel-Becker et al., 2019). Therefore, all key compartments involved in maturation of regulated secretion and its quality control appear to be present and functional at the mammalian synapse.

All the findings discussed above highlight an important principle in secretory and endolysosomal trafficking: compartments can change their Rab identity through compartmental fusion and maturation, and these changes can involve gradual transitions. Consequently, the many studies that rely on identification of compartmental identity using markers like Rabs need to be interpreted with caution; without careful analysis of double- and triple-Rab-labelled cells (Shearer, Petersen, 2019), they may fail to distinguish vital transition stages. Live imaging is required to follow such dynamic changes and in neurons, where additional specialised mechanisms are involved in controlling polarised trafficking (Wang et al., 2024), super-resolution microscopy will almost certainly be critical to confirm that these cells employ the same transitions as non-neuronal cells to generate their DCG compartments. Furthermore, since overexpression of Rabs and other regulators can significantly disrupt secretory trafficking (Corrigan et al., 2014; Fan et al., 2020), employing endogenously labelled proteins, wherever possible (Wells et al., 2023; Stockhammer et al., 2024), is likely to be important in teasing apart the detailed mechanisms involved.

In summary, maturation and quality control steps in the regulated secretory pathway involve compartmental transitions requiring inputs from recycling endosomes and late endosomes respectively (Fig. 3B). These steps can sequentially deliver the secretases involved in APP processing and Aβ formation to regulated secretory compartments. If the resulting compartments are not degraded, this might provide the 'perfect storm' to drive Aβ accumulation (Figs. 3B and 4). But is APP trafficked through the regulated secretory pathway, and if so, does it play a physiological role in these compartments?

4. APP's Roles in DCG Biogenesis and Compartment Maturation

APP and/or its *Drosophila* homologue, APPL, have a range of functions in the nervous system, including regulation of brain development, memory and synaptic functions (Nalivaeva and Turner, 2013), trophic activities (Dawkins and Small, 2014), and intercellular signalling. In the latter case, APP appears to act as a receptor for different Wnts, which control APP stability (Liu et al., 2021), and as a regulator of heterotrimeric G-proteins (Copenhaver, Kögel, 2017), a function activated by Aβ-oligomers and -fibrils (Antonino et al., 2022). More recent work has revealed a potentially conserved role for APP in controlling protein aggregation events in DCG compartments (Singh et al., 2025), an activity that might underpin some of its more general functions in the nervous system highlighted above.

A link between Rab11-positive recycling endosomes, exosome release and both physiological and pathological processing of APP has been suggested by multiple studies in flies and mammals. Genetic studies of the *Drosophila* neuromuscular junction have revealed a key function for Rab11 in pre-synaptic secretion, including release of exosome-like vesicles (Koles et al., 2012; Walsh et al., 2021). This is balanced by the activity of the retromer complex, which controls the sorting of cargos within endosomes. The pre-synaptic Rab11 compartments in this system contain membrane-associated C-terminal fragments of APP (Fig. 1); their levels correlate with Rab11 and increase in neurons that are over-producing exosomes (Walsh et al., 2021; Hendricks et al., 2024). Importantly, studies assessing the effects of AD-associated endolysosomal dysfunction in mammalian neurons also highlight a central role for Rab11 in linking exosomes and Aβ, as well a potential function for the retromer complex (Arbo et al., 2020). Furthermore, there is some overlap between a generic Rab11-exosome protein cargo signature characterised using human cancer cell lines (Singh et al., 2025) and proteins elevated in the cerebrospinal fluid of AD patients (Li et al., 2023), consistent with Rab11-dependent, exosome-associated secretion being induced in AD.

Although most studies of APP have focused on its roles in neurons, there are two other APP-related proteins, APP-like protein 1 (APLP1) and APLP2 in addition to human APP. APP family members are broadly expressed throughout the body and therefore may have general functions that are not neuron-specific. In fact, genetic analysis in *Drosophila* secondary cells reveals that *Drosophila*'s single APP homologue, APPL, is required for normal DCG biogenesis, a function that can be substituted by human APP (Singh et al., 2025) (Fig. 4A).

Like human APP, APPL is a transmembrane protein (Figs. 1 and 4A). Prior to cleavage, its extracellular N-terminal domain is involved in priming DCG protein aggregation, a process regulated by its E1 domain (step '1' in Fig. 4A; Singh et al., 2025). This domain is implicated in Zn^{2+}- and Cu^{2+}-modulated human APP dimerization (August et al., 2019), which may partly explain the established roles of divalent cations in DCG biogenesis (Germanos et al., 2021; Jayawardena et al., 2019). For normal DCG maturation to take place, APPL must then be cleaved, potentially at its β-secretase cleavage site (Fig. 1 and step '2' in Fig. 4A), to dissociate the protein aggregates from membranes and target the APP-CTF to the lysosome (Singh et al., 2025). This lysosomal targeting pathway may involve trafficking to the cell surface and subsequent endocytosis, but alternatively, defective DCG compartments are sometimes targeted via the quality control pathway to LELs (step '3' in Fig. 4A), which are predicted to contain γ-secretase.

Stockhammer et al. (2024) have suggested that recycling endosomes in the regulated secretory pathway may represent a significant proportion of recycling endosomes in the cell. In SCs, APPL must traffic through these compartments and be cleaved by β-secretase to fulfil its functions in DCG biogenesis, and overexpressed APPL also seems to traffic through this pathway at high levels (Singh et al., 2025). As discussed above, APP and BACE1 appear to encounter each other in recycling endosomes of mammalian neurons in a synaptic activity-dependent fashion (Das et al., 2013). Therefore, although the dynamics of APP trafficking through maturing DCG compartments still needs to be assessed in neurons, it seems quite likely that this process will generate physiological levels of APP-βCTF and then Aβ in active neurons (via steps '2' and then '3' in Fig. 4A or by trafficking via the plasma membrane), which are relevant to the reported functions of Aβ (discussed in Brothers et al., 2018).

Disruption of APP processing or APP-dependent DCG aggregation and dissociation events in SCs diverts more compartments towards the degradative arm of the secretory quality control pathway and can lead to accumulation of compartments that, although partially acidified and degraded, fail to traffic normally to lysosomes ('3' in Fig. 4B; Singh et al., 2025). The resulting cells therefore have an endolysosomal trafficking defect characterised by aberrant compartments that have received secretory, recycling and late endosomal/lysosomal inputs, a combination that could promote the pathological build-up of Aβ and/or APP-βCTF (Figs. 3B and 4B).

These findings are consistent with recent reports showing that APP plays a key role in maintaining proteostasis in the brains of ageing flies, mice and humans (Nithianandam et al., 2023) and that overexpressing the β-cleaved C-terminal fragment of APP can induce neuronal toxicity in mammals independently of Aβ (Lauritzen et al., 2016; Vaillant-Beuchot et al., 2021; Bretou et al., 2024; Luo et al., 2025). Indeed, diverting DCG compartments towards the degradation pathway should traffic APP-βCTF to LELs, where it has been shown to induce endolysosomal defects (Kwart et al., 2019; Im et al., 2023), potentially

contributing to neurotoxic pathology. Therefore, even though the model discussed in this review focuses primarily on Aβ generation, the pathological mechanisms discussed could also elevate APP-βCTF, contributing to pathology (see also Section 7).

APPL associates with ILVs in *Drosophila* DCG compartments (Singh et al., 2025). Knockdown of some *ESCRT* (*Endosomal Sorting Complexes Required for Transport*) genes, which are essential for biogenesis of these ILVs, disrupts DCG formation and/or morphology (Marie et al., 2023), suggesting a link between these two intra-compartmental structures. Interestingly, *ESCRT* knockdown suppresses APP-induced neurodegeneration in a fly eye model of AD (Zhuang et al., 2023). Although as with many animal AD studies, this overexpression model does not reflect the pathology in AD patient neurons and will inevitably lack some of the cellular mechanisms operating in human neurons, genetic screens using the *Drosophila* eye have successfully identified conserved suppressor and enhancer functions for genes implicated in AD (Jiang and MacNeil, 2023; Tsintzas and Niccoli, 2024). Therefore, these studies raise the intriguing possibility that AD pathology may involve defects in APP-dependent interactions between ILVs and DCGs.

In conclusion, in non-neuronal cells, APP appears to have a conserved role in controlling membrane-dependent protein aggregation events in Rab11-positive compartments of the regulated secretory pathway. Endolysosomal trafficking defects are induced when this process is disrupted. Neuronal Rab11-positive secretory compartments also play a crucial role in synaptic function and APP processing, with APP critically required for normal proteostasis. So could abnormal secretory compartments with defective lysosomal targeting be the location where mis-processed APP and Aβ initiate AD-associated pathological changes?

5. Aβ, DCG compartment maturation, and the onset of AD-relevant pathologies

Multiple reports suggest that neurodegeneration-inducing effects of Aβ may be mediated via APP (reviewed in Bignante et al., 2013; Kepp, 2016). In fact, recent findings indicate that generation and intracellular accumulation of Aβ may be stimulated via Aβ-oligomer-dependent activation of APP signalling in human Rab11-positive recycling endosomes (Antonino et al., 2022). Indeed, the presence of Aβ-fibrils in mammalian synaptic MVBs (Eckman et al., 2023) and the association of extracellular vesicles with amyloid plaques in AD patient brains (Rajendran et al., 2006; Gilbert et al., 2024) are consistent with a model in which critical events generating Aβ-induced pathologies take place in multivesicular recycling endosomes produced during secretory compartment maturation.

In line with these observations, expression of human Aβ in the secretory system of secondary cells disrupts maturation of DCG compartments (Singh et al., 2025). Indeed, some mutant forms of Aβ that are associated with familial AD strongly inhibit the normal separation of protein aggregates from the DCG compartment limiting membrane and appear to partially block APP cleavage. Related defects are also associated with wild type Aβ expression, but appear more slowly. The defective compartments fuse with smaller acidic compartments, but subsequently, many fail to traffic to the large lysosomes within these cells and they are therefore only partially degraded (Singh et al., 2025) (marked '3' in Fig. 4B).

Membrane-induced protein aggregation in endosomal compartments is not a new concept. It plays a critical role in establishing a protein scaffold formed from proteolytic fragments of the premelanosome (PMEL) protein in human and rodent pigment-containing melanosomes (van Niel et al., 2015). Interestingly, Apolipoprotein E (ApoE), a key genetic risk factor in AD, acts as a regulatory bridge between ILV membranes and the protein scaffold in melanosomes (van Niel et al., 2015). Recently ApoE has been shown to co-localise with Aβ in endosomal compartments of neurites in rodents, with ApoE4, the variant form associated with increased susceptibility to AD, increasing intra-compartmental Aβ levels (Konings et al., 2023). It will be interesting to investigate whether ApoE associates with ILVs and/or membranes in this scenario, since it might help to explain why β-amyloid plaques in patients contain structures resembling complexes between PMEL, ApoE and ILVs in melanosomes (Gilbert et al., 2024).

In Aβ-expressing secondary cells, the contents of defective secretory compartments that fail to be degraded in lysosomes appear to be secreted (step '4' in Fig. 4B) and this material is then abnormally endocytosed by other cells, which also develop endolysosomal defects (Singh et al., 2025). Interestingly, neurotoxic Aβ-oligomers pass between human neurons and glia via a mechanism that also requires exosomes, consistent with the idea that the link between ILVs and aberrantly aggregated proteins in the secretory system might be maintained following secretion (Tong et al., 2024). In other studies, using both flies and mammalian neurons, exosomes and ApoE have both been implicated in mechanisms that not only transfer peroxidated lipids and glucosylceramide from active neurons to glia for detoxification, but also appear to modulate the pathological activities of Aβ (Moulton et al., 2021; Wang et al., 2022). It is tempting to speculate that these protective intercellular communication mechanisms employ the regulated secretory pathway, and that when this pathway is disrupted, it leads to neurotoxicity, while also generating a route to propagate the resulting defects to other cells.

In summary, Aβ can induce endolysosomal pathology within the quality control arm of the regulated secretory trafficking pathway through which it is generated (regulated secretory → recycling endosomal → late endosomal compartments), and this phenotype can then be propagated to other cells. Failure of the APP-dependent dissociation of protein aggregates from membranes induces these pathologies, and may explain why exosomes are implicated in intercellular transfer.

Importantly, an increasing number of AD studies employing neurons derived from human induced pluripotent stem cells (hiPSCs), where high levels of extracellular Aβ, and overexpression of APP or its catabolic products are often not employed, highlight endolysosomal and autophagosomal defects in cells carrying mutations in AD susceptibility loci (eg. Hung, Livesey, 2018; Mishra et al., 2025; Krogsaeter et al., 2025). Indeed, in an hiPSC model for loss-of-function of *SORL1*, an APP trafficking regulator, the observed accumulation of enlarged recycling endosomes, as well as early endosomes (Mishra et al., 2024), is consistent with the phenotypes predicted by defective regulated secretion. Interestingly, specific *SORL1* variants can also enhance Golgi fragmentation in hiPSC models (Haukedal et al., 2023), suggesting that these two AD pathologies affecting different steps in the secretory pathway might be linked. Furthermore, *SORL1* mutation-induced endolysosomal defects can be suppressed by reducing APP levels (Hung et al., 2021), while AD-related endolysosomal defects appear to stimulate release of Aβ-associated exosomes (Eitan et al., 2016), which is again consistent with the model we propose (Figs. 3B and 4). Importantly, hiPSC studies have also highlighted an important role for APP-βCTF in generating AD-associated endolysosomal defects (Kwart et al., 2019), a finding that could also be explained by the model discussed in this article. Indeed, in line with this model (Fig. 4), exosomes are reported to carry elevated levels of APP-CTF in human and animal neuronal models of lysosomal dysfunction and AD (Miranda et al., 2018; Lauritzen et al., 2019; Draper et al., 2026).

To date, many of the primary data supporting the model and underlying mechanisms discussed in this article have been generated using a non-neuronal cell type and by overexpressing AD-related proteins and peptides, as is common in animal models. However, it is important to emphasise that in the SC system, quality control steps in regulated secretion are also disrupted by reduced function of genes involved in DCG biogenesis, most notably APP (Dar et al., 2021; Singh et al., 2025), consistent with APP's role in proteostasis within the brain, conserved from fly to human (Nithianandam et al., 2023). Systems such as secondary cells, in which these steps can be analysed at high resolution, potentially provide the critical stepping stone required to highlight the

specific sub-compartmental events that could trigger endolysosomal pathology and the regulatory inputs that might be modulated to suppress them. These now need to be fully tested in human neurons under less artificial conditions.

6. Where might tau fit in?

If defects in membrane-induced protein aggregation inside DCG compartments initiate early AD pathologies, how could tau, a cytoskeletal regulator residing in the cytosol, also be involved? The endolysosomal trafficking defects associated with AD (Kimura and Yanagisawa, 2018) and the aberrant trafficking in the secretory quality control pathway induced by Aβ (Singh et al., 2025) hint at disrupted interactions between secretory compartments and the cytoskeleton, but could tau participate in this?

There are, in fact, already several reports linking tau to both Aβ and Aβ-oligomers in the endolysosomal system. For example, in rodent neurons, Aβ spreading between cells induces tau hyperphosphorylation via endolysosome-mediated mechanisms (Gao et al., 2025), and Aβ-oligomer assembly in endolysosomes can induce pathological changes in tau's subcellular organisation (Schützmann et al., 2021). The reported involvement of Aβ in the exosomal transfer of pathological tau 'seeds' between human neurons suggests that Aβ/tau interactions may work both ways and be linked to exosomes as well as endosomes (Miyoshi et al., 2021). Whether these interactions take place inside DCG compartments that have failed to mature properly is now a critical question. In this regard, the observation that in mouse neurons, tau accumulation disrupts activity of IST1, an accessory ESCRT-III protein implicated in Rab11a-exosome biogenesis (Marie et al., 2023), suggests a tantalising link to recycling endosomal secretory compartments (Feng et al., 2020).

Could there be other molecular connections between tau and APP-derived cleavage products that implicate the endolysosomal system and exosome biogenesis? Interestingly, APP-βCTF, Aβ and tau have all been shown to bind to components of the V-ATPase proton pump, a transmembrane complex associated with recycling and late endosomes, as well as lysosomes (Kim et al., 2023; Im et al., 2023).

But perhaps one of the most exciting candidates that might link tau and Aβ is activity-regulated cytoskeleton-associated protein, ARC (or ARC1 in *Drosophila*). This protein, which has a well-established, conserved role in synaptic plasticity (Sullivan et al., 2025), is elevated in the brains of AD patients versus healthy controls (Wu et al., 2011). Furthermore, some genetic variants of *Arc* are associated with increased AD risk (Landgren et al., 2012; Bi et al., 2018). In flies, elevated tau levels induce increased ARC1 expression and tau-induced neurodegeneration is suppressed by *Arc1* knockdown or mutation (Schulz et al., 2023). Another important property of ARC is that it contains a viral-like Gag domain, which can assemble into mRNA-containing capsid structures within ILVs at pre-synaptic termini (Ashley et al., 2018). Furthermore, mammalian Arc can bind to the cytoplasmic domain of APP (Lee et al., 2023) and genetically impacts the generation of secreted EVs associated with APP processing and Aβ (Arbo et al., 2020). Therefore, ARC appears to provide a cytoskeletal link between tau, exosomes, APP, Aβ and AD. Since its proposed roles in synaptic plasticity and RNA transfer across the synapse (Sullivan et al., 2025) are likely to involve the regulated secretory pathway, more detailed investigation of ARC's functions in regulated secretion and intercellular communication, both in healthy and Aβ-/tau-modulated cells, now seems essential.

7. Concluding Remarks and Future Perspectives

The recent discovery that DCG compartments mature in an APP-dependent manner through transition to recycling endosomal identity, and can subsequently receive late endosomal/lysosomal inputs, which in response to AD-relevant genetic manipulations induce endolysosomal and secretory defects (Fig. 4B), has suggested a new conceptual framework to explain the initial triggering of AD pathology. It predicts that in sporadic disease, progressive accumulation of defective protein aggregates in secretory compartments of ageing neurons could promote pathological changes in Aβ generation and reorganisation of interacting cytoskeletal tau that exacerbates these phenotypes further.

Interestingly, in this model, pathological changes reflect defects in a fundamental cell biological process that probably occurs across many or all animal tissues. However, long-lived neurons with their unique secretory morphology may be particularly susceptible to these changes. The well-established role of autophagy in AD and other neurodegenerative diseases (Oettinger and Yamamoto, 2025) aligns well with the model and suggests that a better understanding of autophagy's roles in DCG compartment quality control may provide more insights into possible therapeutic interventions. Furthermore, the recent reports that APP C-terminal fragments generated following β-secretase cleavage accumulate at synapses in AD (Ferrer-Raventós et al., 2023) and can independently induce AD pathology (Lauritzen et al., 2016; Vaillant-Beuchot et al., 2021; Bretou et al., 2024; Yeapuri et al., 2025; Luo et al., 2025; Vrancx and Annaert, 2025) are also compatible with the idea that maturing recycling endosomal DCG compartments might be the origin of pathological events that trigger neurodegeneration.

Notably, genes implicated in other neurodegenerative diseases also appear to play key roles in Rab11-positive endosomes and DCG compartment maturation. For example, *CHMP2B* and *CHMP1A*, two *ESCRT*s regulating Rab11-exosome biogenesis (Marie et al., 2023), are associated with frontotemporal dementia and hereditary spastic paraplegia respectively (Urwin et al., 2009; Reid et al., 2005). Furthermore, Rab11 compartments have been implicated in pathological events linked to amyotrophic lateral sclerosis- (ALS-) associated TDP-43 (Deshpande et al., 2016), Parkinson's-associated α-synuclein (Breda et al., 2015) and Huntington's Disease (Giorgini and Steinert, 2013) in *Drosophila* disease models. Therefore, detailed analysis of maturation events in the regulated secretory pathway in these diseases may reveal some common principles and determine the potential for disease-specific targeting of individual steps.

So how might the advances considered in this article be pursued further and impact on the AD field in the future? As discussed above, there are several genetic and molecular players associated with AD, such as tau, ApoE and ARC1, whose roles in regulated secretion within *Drosophila* secondary cells now need detailed investigation (Fig. 4A). In these cells, the *Arc1* gene appears to be expressed at particularly high levels (Immarigeon et al., 2021). If ARC1 and tau do modulate ILV and/or DCG biogenesis and endolysosomal trafficking during secretory compartment maturation, this would suggest a fascinating link between the cytosolic cytoskeleton and the intra-compartmental events that appear to be affected by other AD-related genetic manipulations. The different phenotypes induced by Aβ in secondary cells, including DCG mis-assembly, endolysosomal trafficking defects and the intercellular propagation of these defects can all be screened for genetic modifiers and then those modifiers tested in established Aβ-induced neurodegenerative models in the fly to assess their disease relevance.

A central objective going forward will be to exploit state-of-the-art high-resolution live-cell imaging techniques to better characterise DCG maturation and quality control steps in mammalian models and hiPSC systems, focusing particularly on differentiated neurons. AD studies in hiPSCs have already highlighted endolysosomal and autophagic trafficking defects as common phenotypes in patient-derived and genetically manipulated neurons (Mishra et al., 2024; Maninger et al., 2024; Odonchimed et al., 2026), but the initiating mechanisms remain unclear. In these systems, the use of endogenously expressed tagged markers and the characterisation of Rab transitions during secretory maturation will be critical. In this context, identifying neuronal DCG cargos, such as neuropeptides, that can also be endogenously labelled should help to identify the compartments and assess their targeting for lysosomal degradation during quality control. Once these maturation

steps are characterised and analysed in AD models that are generated from patients or via genome-editing, it should be possible to determine their genetic regulation, informed by genetic modifier studies in simpler organisms, to pinpoint cross-species parallels and differences. As in the fly system, robust modifiers could then be tested in mammalian AD neurodegeneration models to identify which pathological steps might be good therapeutic targets.

Mammalian and fly data suggest that Rab11a-exosome loading and secretion might be misregulated in AD patients and AD animal models (Li et al., 2023; Arbo et al., 2020; Singh et al., 2025), and that this may be relevant to intercellular propagation of endolysosomal trafficking defects (Tong et al., 2024). In addition to their potential functional importance, these findings suggest that Rab11-exosomes may be useful AD biomarkers. Surface markers specific for this exosome subtype are currently limited (Mason et al., 2024), so identifying new ones, particularly on neuronal Rab11-exosomes, will be critical to test this hypothesis.

Finally, a potentially important take-home message from the studies considered in this article, is that the dynamic nature of secretory biology, and in particular events occurring inside secretory compartments, might be central to identifying hub-like processes that unite the diverse genetic and molecular players associated with AD. Given the complexity of these processes, if they can be better characterised, they may not only suggest novel therapies and new biomarker assays, but they may also allow us to categorise multiple sub-classes of disease and consequently suggest more personalised treatment strategies for patients in the clinic.

CRediT authorship contribution statement

Clive Wilson: Writing – original draft, Funding acquisition, Formal analysis, Conceptualization. **Deborah C I Goberdhan:** Writing – original draft, Funding acquisition, Formal analysis, Conceptualization. **Preman Singh:** Writing – review & editing, Formal analysis, Conceptualization. **Bhavna Verma:** Writing – review & editing, Formal analysis, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.pneurobio.2026.102926.

References

Alberts, B., Johnson, A., Lewis, J., Raff, M., Roberts, K., Walter, P., 2002. Molecular Biology of the Cell, 4th ed.). Garland Science, New York.

Ando, K., Houben, S., Homa, M., de Fisenne, M.A., Potier, M.C., Erneux, C., Brion, J.P., Leroy, K., 2021. Alzheimer's disease: tau pathology and dysfunction of endocytosis. Front Mol. Neurosci. 13, 583755. https://doi.org/10.3389/fnmol.2020.583755.

Antonino, M., Marmo, P., Freites, C.L., Quassollo, G.E., Sánchez, M.F., Lorenzo, A., Bignante, E.A., 2022. Aβ assemblies promote amyloidogenic processing of APP and intracellular accumulation of Aβ42 Through Go/Gβγ Signaling. Front Cell Dev. Biol. 10, 852738. https://doi.org/10.3389/fcell.2022.852738.

Arbo, B.D., Cechinel, L.R., Palazzo, R.P., Siqueira, I.R., 2020. Endosomal dysfunction impacts extracellular vesicle release: central role in Aβ pathology. Ageing Res Rev. 58, 101006. https://doi.org/10.1016/j.arr.2019.101006.

Ashley, J., Cordy, B., Lucia, D., Fradkin, L.G., Budnik, V., Thomson, T., 2018. Retrovirus-like gag protein arc1 binds rna and traffics across synaptic boutons. Cell 172, 262–274.e11. https://doi.org/10.1016/j.cell.2017.12.022.

August, A., Schmidt, N., Klingler, J., Baumkötter, F., Lechner, M., Klement, J., Eggert, S., Vargas, C., Wild, K., Keller, S., Kins, S., 2019. Copper and zinc ions govern the trans-directed dimerization of APP family members in multiple ways. J. Neurochem. 151, 626–641. https://doi.org/10.1111/jnc.14716.

Beronja, S., Laprise, P., Papoulas, O., Pellikka, M., Sisson, J., Tepass, U., 2005. Essential function of *Drosophila* Sec6 in apical exocytosis of epithelial photoreceptor cells. J. Cell Biol. 169, 635–646. https://doi.org/10.1083/jcb.200410081.

Bi, R., Kong, L.L., Xu, M., Li, G.D., Zhang, D.F., Alzheimer's Disease Neuroimaging Initiative, Li, T., Fang, Y., Zhang, C., Zhang, B., Yao, Y.G., 2018. The *Arc* Gene Confers Genetic Susceptibility to Alzheimer's Disease in Han Chinese. Mol. Neurobiol. 55, 1217–1226. https://doi.org/10.1007/s12035-017-0397-6.

Bignante, E.A., Heredia, F., Morfini, G., Lorenzo, A., 2013. Amyloid β precursor protein as a molecular target for amyloid β-induced neuronal degeneration in Alzheimer's disease. Neurobiol. Aging 34, 2525–2537. https://doi.org/10.1016/j.neurobiolaging.2013.04.021.

Boda, A., Varga, L.P., Nagy, A., Szenci, G., Csizmadia, T., Lőrincz, P., Juhász, G., 2023. Rab26 controls secretory granule maturation and breakdown in *Drosophila*. Cell Mol. Life Sci. 80, 24. https://doi.org/10.1007/s00018-022-04674-8.

Breda, C., Nugent, M.L., Estranero, J.G., Kyriacou, C.P., Outeiro, T.F., Steinert, J.R., Giorgini, F., 2015. Rab11 modulates α-synuclein-mediated defects in synaptic transmission and behaviour. Hum. Mol. Genet 24, 1077–1091. https://doi.org/10.1093/hmg/ddu521.

Bretou, M., Sannerud, R., Escamilla-Ayala, A., Leroy, T., Vrancx, C., Van Acker, Z.P., Perdok, A., Vermeire, W., Vorsters, I., Van Keymolen, S., Maxson, M., Pavie, B., Wierda, K., Eskelinen, E.L., Annaert, W., 2024. Accumulation of APP C-terminal fragments causes endolysosomal dysfunction through the dysregulation of late endosome to lysosome-ER contact sites. Dev. Cell 59, 1571–1592.e9. https://doi.org/10.1016/j.devcel.2024.03.030.

Brothers, H.M., Gosztyla, M.L., Robinson, S.R., 2018. The physiological roles of amyloid-β peptide hint at new ways to treat Alzheimer's Disease. Front Aging Neurosci. 10, 118. https://doi.org/10.3389/fnagi.2018.00118.

Buggia-Prévot, V., Fernandez, C.G., Riordan, S., Vetrivel, K.S., Roseman, J., Waters, J., Bindokas, V.P., Vassar, R., Thinakaran, G., 2014. Axonal BACE1 dynamics and targeting in hippocampal neurons: a role for Rab11 GTPase. Mol. Neurodegener. 9 (1). https://doi.org/10.1186/1750-1326-9-1.

Cataldo, A.M., Hamilton, D.J., Barnett, J.L., Paskevich, P.A., Nixon, R.A., 1996. Properties of the endosomal-lysosomal system in the human central nervous system: disturbances mark most neurons in populations at risk to degenerate in Alzheimer's disease. J. Neurosci. 16, 186–199. https://doi.org/10.1523/JNEUROSCI.16-01-00186.1996.

Copenhaver, P.F., Kögel, D., 2017. Role of APP Interactions with Heterotrimeric G Proteins: Physiological Functions and Pathological Consequences. Front Mol. Neurosci. 10, 3. https://doi.org/10.3389/fnmol.2017.00003.

Corrigan, L., Redhai, S., Leiblich, A., Fan, S.J., Perera, S.M., Patel, R., Gandy, C., Wainwright, S.M., Morris, J.F., Hamdy, F., Goberdhan, D.C., Wilson, C., 2014. BMP-regulated exosomes from *Drosophila* male reproductive glands reprogram female behavior. J Cell Biol. 206 (5), 671–688. https://doi.org/10.1083/jcb.201401072.

Dar, G.H., Mendes, C.C., Kuan, W.L., Speciale, A.A., Conceição, M., Görgens, A., Uliyakina, I., Lobo, M.J., Lim, W.F., El Andaloussi, S., Mäger, I., Roberts, T.C., Barker, R.A., Goberdhan, D.C.I., Wilson, C., Wood, M.J.A., 2021. GAPDH controls extracellular vesicle biogenesis and enhances the therapeutic potential of EV mediated siRNA delivery to the brain. Nat. Commun. 12, 6666. https://doi.org/10.1038/s41467-021-27056-3.

Das, U., Scott, D.A., Ganguly, A., Koo, E.H., Tang, Y., Roy, S., 2013. Activity-induced convergence of APP and BACE-1 in acidic microdomains via an endocytosis-dependent pathway. Neuron 79, 447–460. https://doi.org/10.1016/j.neuron.2013.05.035.

Das, U., Wang, L., Ganguly, A., Saikia, J.M., Wagner, S.L., Koo, E.H., Roy, S., 2016. Visualizing APP and BACE-1 approximation in neurons yields insight into the amyloidogenic pathway. Nat. Neurosci. 19, 55–64. https://doi.org/10.1038/nn.4188.

Dawkins, E., Small, D.H., 2014. Insights into the physiological function of the β-amyloid precursor protein: beyond Alzheimer's disease. J. Neurochem. 129, 756–769. https://doi.org/10.1111/jnc.12675.

Deng, Q., Wu, C., Parker, E., Liu, T.C., Duan, R., Yang, L., 2024. Microglia and Astrocytes in Alzheimer's Disease: Significance and Summary of Recent Advances. Aging Dis. 15, 1537–1564. https://doi.org/10.14336/AD.2023.0907.

Deshpande, M., Feiger, Z., Shilton, A.K., Luo, C.C., Silverman, E., Rodal, A.A., 2016. Role of BMP receptor traffic in synaptic growth defects in an ALS model. Mol. Biol. Cell 27, 2898–2910. https://doi.org/10.1091/mbc.E16-07-0519.

Dinkins, M.B., Enasko, J., Hernandez, C., Wang, G., Kong, J., Helwa, I., Liu, Y., Terry, A. V., Jr, Bieberich, E., 2016. Neutral sphingomyelinase-2 deficiency ameliorates alzheimer's disease pathology and improves cognition in the 5XFAD Mouse. J. Neurosci. 36, 8653–8667. https://doi.org/10.1523/JNEUROSCI.1429-16.2016.

Dixson, A.C., Dawson, T.R., Di Vizio, D., Weaver, A.M., 2023. Context-specific regulation of extracellular vesicle biogenesis and cargo selection (m). Nat. Rev. Mol. Cell Biol. 24, 454–476. https://doi.org/10.1038/s41580-023-00576-0.

Draper, D., George, A.E., Veenendaal, T., van Dijk, S., Soltani, E.Z., Sanzà, P., Verweij, F. J., Klumperman, J., Farías, G.G., 2026. HOPS disruption impairs APP trafficking and processing, promoting exosomal secretion of APP-CTFs. Neurobiol. Dis. 219, 107269. https://doi.org/10.1016/j.nbd.2026.107269.

Eckman, E.A., Clausen, D.M., Solé-Domènech, S., Lee, C.W., Sinobas-Pereira, C., Domalewski, R.J., Nichols, M.R., Pacheco-Quinto, J., 2023. Nascent Aβ42 Fibrillization in Synaptic Endosomes Precedes Plaque Formation in a Mouse Model of Alzheimer's-like β-Amyloidosis. J. Neurosci. 43, 8812–8824. https://doi.org/10.1523/JNEUROSCI.1318-23.2023.

Eitan, E., Hutchison, E.R., Marosi, K., Comotto, J., Mustapic, M., Nigam, S.M., Suire, C., Maharana, C., Jicha, G.A., Liu, D., Machairaki, V., Witwer, K.W., Kapogiannis, D., Mattson, M.P., 2016. Extracellular vesicle-associated Aβ mediates trans-neuronal bioenergetic and Ca^{2+}-handling deficits in Alzheimer's Disease models. NPJ Aging Mech. Dis. 2, 16019. https://doi.org/10.1038/npjamd.2016.19.

Fan, S.J., Kroeger, B., Marie, P.P., Bridges, E.M., Mason, J.D., McCormick, K., Zois, C.E., Sheldon, H., Khalid Alham, N., Johnson, E., Ellis, M., Stefana, M.I., Mendes, C.C., Wainwright, S.M., Cunningham, C., Hamdy, F.C., Morris, J.F., Harris, A.L., Wilson, C., Goberdhan, D.C., 2020. Glutamine deprivation alters the origin and function of cancer cell exosomes. EMBO J. 39, e103009. https://doi.org/10.15252/embj.2019103009.

Farfel-Becker, T., Roney, J.C., Cheng, X.T., Li, S., Cuddy, S.R., Sheng, Z.H., 2019. Neuronal Soma-Derived Degradative Lysosomes Are Continuously Delivered to Distal Axons to Maintain Local Degradation Capacity. Cell Rep. 28, 51–64.e4. https://doi.org/10.1016/j.celrep.2019.06.013.

Feng, Q., Luo, Y., Zhang, X.N., Yang, X.F., Hong, X.Y., Sun, D.S., Li, X.C., Hu, Y., Li, X.G., Zhang, J.F., Li, X., Yang, Y., Wang, Q., Liu, G.P., Wang, J.Z., 2020. MAPT/Tau accumulation represses autophagy flux by disrupting IST1-regulated ESCRT-III complex formation: a vicious cycle in Alzheimer neurodegeneration. Autophagy 16, 641–658. https://doi.org/10.1080/15548627.2019.1633862.

Ferrer-Raventós, P., Puertollano-Martín, D., Querol-Vilaseca, M., Sánchez-Aced, É., Valle-Tamayo, N., Cervantes-Gonzalez, A., Nuñez-Llaves, R., Pegueroles, J., Dols-Icardo, O., Iulita, M.F., Aldecoa, I., Molina-Porcel, L., Sánchez-Valle, R., Fortea, J., Belbin, O., Sirisi, S., Lleó, A., 2023. Amyloid precursor protein *β*CTF accumulates in synapses in sporadic and genetic forms of Alzheimer's disease. Neuropathol. Appl. Neurobiol. 49, e12879. https://doi.org/10.1111/nan.12879.

Fourriere, L., Gleeson, P.A., 2026. The dynamic role of the Golgi apparatus in neuronal function and Alzheimer's Disease. Subcell. Biochem 111, 441–462. https://doi.org/10.1007/978-3-032-16833-7_18.

Gao, Y., Wang, L., Doeswijk, T., Winblad, B., Schedin-Weiss, S., Tjernberg, L.O., 2025. Intraneuronal Aβ accumulation causes tau hyperphosphorylation via endolysosomal leakage. Alzheimers Dement 21, e70091. https://doi.org/10.1002/alz.70091.

Germanos, M., Gao, A., Taper, M., Yau, B., Kebede, M.A., 2021. Inside the Insulin Secretory Granule. Metabolites 11, 515. https://doi.org/10.3390/metabo11080515.

Gilbert, M.A.G., Fatima, N., Jenkins, J., O'Sullivan, T.J., Schertel, A., Halfon, Y., Wilkinson, M., Morrema, T.H.J., Geibel, M., Read, R.J., Ranson, N.A., Radford, S.E., Hoozemans, J.J.M., Frank, R.A.W., 2024. CryoET of β-amyloid and tau within postmortem Alzheimer's disease brain. Nature 631, 913–919. https://doi.org/10.1038/s41586-024-07680-x.

Giorgini, F., Steinert, J.R., 2013. Rab11 as a modulator of synaptic transmission. Commun. Integr. Biol. 6, e26807. https://doi.org/10.4161/cib.26807.

Goberdhan, D.C.I., Harris, A.L., Wilson, C., 2026. Generating exosome subtypes: diverse membrane origins and marriages. Trends Cell Biol. In press. ⟨https://www.sciencedirect.com/science/article/pii/S0962892426000401.⟩.

Gondré-Lewis, M.C., Park, J.J., Loh, Y.P., 2012. Cellular mechanisms for the biogenesis and transport of synaptic and dense-core vesicles. Int Rev. Cell Mol. Biol. 299, 27–115. https://doi.org/10.1016/B978-0-12-394310-1.00002-3.

Guillaumin, M.C.C., Burdakov, D., 2021. Neuropeptides as Primary Mediators of Brain Circuit Connectivity. Front Neurosci. 15, 644313. https://doi.org/10.3389/fnins.2021.644313.

Gustavsson, A., Norton, N., Fast, T., Frölich, L., Georges, J., Holzapfel, D., Kirabali, T., Krolak-Salmon, P., Rossini, P.M., Ferretti, M.T., Lanman, L., Chadha, A.S., van der Flier, W.M., 2023. Global estimates on the number of persons across the Alzheimer's disease continuum. Alzheimers Dement 19, 658–670. https://doi.org/10.1002/alz.12694.

Haukedal, H., Corsi, G.I., Gadekar, V.P., Doncheva, N.T., Kedia, S., de Haan, N., Chandrasekaran, A., Jensen, P., Schiønning, P., Vallin, S., Marlet, F.R., Poon, A., Pires, C., Agha, F.K., Wandall, H.H., Cirera, S., Simonsen, A.H., Wandall, T.T., Nielsen, J.E., Hyttel, P., Muddashetty, R., Aldana, B.I., Gorodkin, J., Nair, D., Meyer, M., Larsen, M.R., Freude, K., 2023. Golgi fragmentation - One of the earliest organelle phenotypes in Alzheimer's Disease neurons. Front Neurosci. 17, 1120086. https://doi.org/10.3389/fnins.2023.1120086.

Hendricks, E.L., Linskey, N., Smith, I.R., Liebl, F.L.W., 2024. Kismet/CHD7/CHD8 and amyloid precursor protein-like regulate synaptic levels of Rab11 at the *Drosophila* neuromuscular junction. Int J. Mol. Sci. 25, 8429. https://doi.org/10.3390/ijms25158429.

Hevesi, Z., Hökfelt, T., Harkany, T., 2025. Neuropeptides: the evergreen jack-of-all-trades in neuronal circuit development and regulation. Bioessays 47, e202400238. https://doi.org/10.1002/bies.202400238.

Hung, C., Tuck, E., Stubbs, V., van der Lee, S.J., Aalfs, C., van Spaendonk, R., Scheltens, P., Hardy, J., Holstege, H., Livesey, F.J., 2021. *SORL1* deficiency in human excitatory neurons causes APP-dependent defects in the endolysosome-autophagy network. Cell Rep. 35, 109259. https://doi.org/10.1016/j.celrep.2021.109259.

Hung, C.O.Y., Livesey, F.J., 2018. Altered γ-secretase processing of APP disrupts lysosome and autophagosome function in monogenic Alzheimer's Disease. Cell Rep. 25, 3647–3660.e2. https://doi.org/10.1016/j.celrep.2018.11.095.

Im, E., Jiang, Y., Stavrides, P.H., Darji, S., Erdjument-Bromage, H., Neubert, T.A., Choi, J. Y., Wegiel, J., Lee, J.H., Nixon, R.A., 2023. Lysosomal dysfunction in Down syndrome and Alzheimer mouse models is caused by v-ATPase inhibition by Tyr682-phosphorylated APP βCTF. Sci. Adv. 9, eadg1925. https://doi.org/10.1126/sciadv.adg1925.

Immarigeon, C., Frei, Y., Delbare, S.Y.N., Gligorov, D., Machado Almeida, P., Grey, J., Fabbro, L., Nagoshi, E., Billeter, J.C., Wolfner, M.F., Karch, F., Maeda, R.K., 2021. Identification of a micropeptide and multiple secondary cell genes that modulate *Drosophila* male reproductive success. Proc. Natl. Acad. Sci. Usa. 118, e2001897118. https://doi.org/10.1073/pnas.2001897118.

Ivanova, D., Cousin, M.A., 2022. Synaptic Vesicle Recycling and the Endolysosomal System: A Reappraisal of Form and Function. Front Synaptic Neurosci. 14, 826098. https://doi.org/10.3389/fnsyn.2022.826098.

Januário, Y.C., Eden, J., de Oliveira, L.S., De Pace, R., Tavares, L.A., da Silva-Januário, M.E., Apolloni, V.B., Wilby, E.L., Altmeyer, R., Burgos, P.V., Corrêa, S.A.L., Gershlick, D.C., daSilva, L.L.P., 2022. Clathrin adaptor AP-1-mediated Golgi export of amyloid precursor protein is crucial for the production of neurotoxic amyloid fragments. J. Biol. Chem. 298, 102172. https://doi.org/10.1016/j.jbc.2022.102172.

Jayawardena, B.M., Jones, M.R., Hong, Y., Jones, C.E., 2019. Copper ions trigger disassembly of neurokinin B functional amyloid and inhibit de novo assembly. J. Struct. Biol. 208, 107394. https://doi.org/10.1016/j.jsb.2019.09.011.

Jiang, Y., MacNeil, L.T., 2023. Simple model systems reveal conserved mechanisms of Alzheimer's disease and related tauopathies. Mol. Neurodegener. 18, 82. https://doi.org/10.1186/s13024-023-00664-x.

Kang, C.J., Guzmán-Clavel, L.E., Lei, K., Koo, M., To, S., Roche, J.P., 2024. The exocyst subunit Sec15 is critical for proper synaptic development and function at the *Drosophila* NMJ. Mol. Cell Neurosci. 128, 103914. https://doi.org/10.1016/j.mcn.2023.103914.

Kepp, K.P., 2016. Alzheimer's disease due to loss of function: A new synthesis of the available data. Prog. Neurobiol. 143, 36–60. https://doi.org/10.1016/j.pneurobio.2016.06.004.

Khvotchev, M.V., Ren, M., Takamori, S., Jahn, R., Südhof, T.C., 2003. Divergent functions of neuronal Rab11b in Ca2+-regulated versus constitutive exocytosis. J. Neurosci. 23, 10531–10539. https://doi.org/10.1523/JNEUROSCI.23-33-10531.2003.

Kim, B.H., Kim, S., Nam, Y., Park, Y.H., Shin, S.M., Moon, M., 2025. Second-generation anti-amyloid monoclonal antibodies for Alzheimer's disease: current landscape and future perspectives. Transl. Neurodegener. 14, 6. https://doi.org/10.1186/s40035-025-00465-w.

Kim, S.H., Cho, Y.S., Kim, Y., Park, J., Yoo, S.M., Gwak, J., Kim, Y., Gwon, Y., Kam, T.I., Jung, Y.K., 2023. Endolysosomal impairment by binding of amyloid beta or MAPT/Tau to V-ATPase and rescue via the HYAL-CD44 axis in Alzheimer disease (Aug). Autophagy 19 (8), 2318–2337. https://doi.org/10.1080/15548627.2023.2181614.

Kimura, N., Yanagisawa, K., 2018. Traffic jam hypothesis: Relationship between endocytic dysfunction and Alzheimer's disease. Neurochem. Int 119, 35–41. https://doi.org/10.1016/j.neuint.2017.07.002.

Kokotos, A.C., Peltier, J., Davenport, E.C., Trost, M., Cousin, M.A., 2018. Activity-dependent bulk endocytosis proteome reveals a key presynaptic role for the monomeric GTPase Rab11. Proc. Natl. Acad. Sci. Usa. 115, E10177–E10186. https://doi.org/10.1073/pnas.1809189115.

Koles, K., Nunnari, J., Korkut, C., Barria, R., Brewer, C., Li, Y., Leszyk, J., Zhang, B., Budnik, V., 2012. Mechanism of evenness interrupted (Evi)-exosome release at synaptic boutons. J. Biol. Chem. 287, 16820–16834. https://doi.org/10.1074/jbc.M112.342667.

Konings, S.C., Nyberg, E., Martinsson, I., Torres-Garcia, L., Klementieva, O., Guimas Almeida, C., Gouras, G.K., 2023. Apolipoprotein E intersects with amyloid-β within neurons. Life Sci. Alliance 6, e202201887. https://doi.org/10.26508/lsa.202201887.

Krogsaeter, E.K., McKetney, J., Valiente-Banuet, L., Marquez, A., Willis, A., Cakir, Z., Stevenson, E., Jang, G.M., Rao, A., Li, E., Zhou, A., Attili, A., Chang, T.S., Kampmann, M., Huang, Y., Krogan, N.J., Swaney, D.L., 2025. Lysosomal proteomics reveals mechanisms of neuronal APOE4-associated lysosomal dysfunction. Autophagy 21, 3240–3265. https://doi.org/10.1080/15548627.2025.2576613.

Kwart, D., Gregg, A., Scheckel, C., Murphy, E.A., Paquet, D., Duffield, M., Fak, J., Olsen, O., Darnell, R.B., Tessier-Lavigne, M., 2019. A large panel of isogenic *APP* and *PSEN1* mutant human iPSC neurons reveals shared endosomal abnormalities mediated by APP β-CTFs, not Aβ. Neuron 104, 256–270.e5. https://doi.org/10.1016/j.neuron.2019.07.010.

Landgren, S., von Otter, M., Palmér, M.S., Zetterström, C., Nilsson, S., Skoog, I., Gustafson, D.R., Minthon, L., Wallin, A., Andreasen, N., Bogdanovic, N., Marcusson, J., Blennow, K., Zetterberg, H., Kettunen, P., 2012. A novel ARC gene polymorphism is associated with reduced risk of Alzheimer's disease. J. Neural Transm. (Vienna) 119, 833–842. https://doi.org/10.1007/s00702-012-0823-x.

Lauritzen, I., Pardossi-Piquard, R., Bourgeois, A., Pagnotta, S., Biferi, M.G., Barkats, M., Lacor, P., Klein, W., Bauer, C., Checler, F., 2016. Intraneuronal aggregation of the β-CTF fragment of APP (C99) induces Aβ-independent lysosomal-autophagic pathology. Acta Neuropathol. 132, 257–276. https://doi.org/10.1007/s00401-016-1577-6.

Lauritzen, I., Bécot, A., Bourgeois, A., Pardossi-Piquard, R., Biferi, M.G., Barkats, M., Checler, F., 2019. Targeting γ-secretase triggers the selective enrichment of oligomeric APP-CTFs in brain extracellular vesicles from Alzheimer cell and mouse models. Transl. Neurodegener. 8, 35. https://doi.org/10.1186/s40035-019-0176-6.

Lee, P.H., Anaya, M., Ladinsky, M.S., Reitsma, J.M., Zinn, K., 2023. An extracellular vesicle targeting ligand that binds to Arc proteins and facilitates Arc transport in vivo. Elife 12, e82874. https://doi.org/10.7554/eLife.82874.
Li, M., Feng, F., Feng, H., Hu, P., Xue, Y., Xu, T., Song, E., 2022. VAMP4 regulates insulin levels by targeting secretory granules to lysosomes. J. Cell Biol. 221, e202110164. https://doi.org/10.1083/jcb.202110164.
Li, Y., Chen, Z., Wang, Q., Lv, X., Cheng, Z., Wu, Y., Tang, F., Shen, Y., Gao, F., 2023. Identification of hub proteins in cerebrospinal fluid as potential biomarkers of Alzheimer's disease by integrated bioinformatics. J. Neurol. 270, 1487–1500. https://doi.org/10.1007/s00415-022-11476-2.
Liu, T., Zhang, T., Nicolas, M., Boussicault, L., Rice, H., Soldano, A., Claeys, A., Petrova, I., Fradkin, L., De Strooper, B., Potier, M.C., Hassan, B.A., 2021. The amyloid precursor protein is a conserved Wnt receptor. Elife 10, e69199. https://doi.org/10.7554/eLife.69199.
Luo, M., Zhou, J., Sun, C., Chen, W., Fu, C., Si, C., Zhang, Y., Geng, Y., Chen, Y., 2025. APP β-CTF triggers cell-autonomous synaptic toxicity independent of Aβ. Elife 13, RP100968. https://doi.org/10.7554/eLife.100968.
Mamde, S., Rose, S.E., Prater, K.E., Cochoit, A., Lin, Y.F., Smith, I., Johnson, C.S., Reid, A. N., Qiu, W., Strohbehn, S., Keene, C.D., Lee, S.I., Lin, K.Z., Rolf, B.A., Garden, G.A., Blue, E.E., Young, J.E., Jayadev, S., 2025. Genetic risk implicating endolysosomal network genes correlates with endolysosomal dysfunction across neural cell types in Alzheimer's disease. bioRxiv 2025 03 (16), 643481.
Maninger, J.K., Nowak, K., Goberdhan, S., O'Donoghue, R., Connor-Robson, N., 2024. Cell type-specific functions of Alzheimer's disease endocytic risk genes. Philos. Trans. R. Soc. Lond. B Biol. Sci. 379 (1899), 20220378. https://doi.org/10.1098/rstb.2022.0378.
Marie, P.P., Fan, S.J., Mason, J., Wells, A., Mendes, C.C., Wainwright, S.M., Scott, S., Fischer, R., Harris, A.L., Wilson, C., Goberdhan, D.C.I., 2023. Accessory ESCRT-III proteins are conserved and selective regulators of Rab11a-exosome formation. J. Extra Vesicles 12, e12311. https://doi.org/10.1002/jev2.12311.
Mason, J.D., Marks, E., Fan, S.J., McCormick, K., Wilson, C., Harris, A.L., Hamdy, F.C., Cunningham, C., Goberdhan, D.C.I., 2024. Stress-induced Rab11a-exosomes induce amphiregulin-mediated cetuximab resistance in colorectal cancer. J. Extra Vesicles 13, e12465. https://doi.org/10.1002/jev2.12465.
Maxfield, F.R., McGraw, T.E., 2004. Endocytic recycling. Nat. Rev. Mol. Cell Biol. 5, 121–132. https://doi.org/10.1038/nrm1315.
Miranda, A.M., Lasiecka, Z.M., Xu, Y., Neufeld, J., Shahriar, S., Simoes, S., Chan, R.B., Oliveira, T.G., Small, S.A., Di Paolo, G., 2018. Neuronal lysosomal dysfunction releases exosomes harboring APP C-terminal fragments and unique lipid signatures. Nat. Commun. 9, 291. https://doi.org/10.1038/s41467-017-02533-w.
Mishra, A.K., Tripathi, M.K., Kumar, D., Gupta, S.P., 2025. Neurons Specialize in Presynaptic Autophagy: A Perspective to Ameliorate Neurodegeneration. Mol. Neurobiol. 62, 2626–2640. https://doi.org/10.1007/s12035-024-04399-8.
Mishra, S., Jayadev, S., Young, J.E., 2024. Differential effects of SORL1 deficiency on the endo-lysosomal network in human neurons and microglia. Philos. Trans. R. Soc. Lond. B Biol. Sci. 379 (1899), 20220389. https://doi.org/10.1098/rstb.2022.0389.
Miyoshi, E., Bilousova, T., Melnik, M., Fakhrutdinov, D., Poon, W.W., Vinters, H.V., Miller, C.A., Corrada, M., Kawas, C., Bohannan, R., Caraway, C., Elias, C., Maina, K. N., Campagna, J.J., John, V., Gylys, K.H., 2021. Exosomal tau with seeding activity is released from Alzheimer's disease synapses, and seeding potential is associated with amyloid beta. Lab Invest 101, 1605–1617. https://doi.org/10.1038/s41374-021-00644-z.
Morris, G.P., Clark, I.A., Vissel, B., 2014. Inconsistencies and controversies surrounding the amyloid hypothesis of Alzheimer's disease. Acta Neuropathol. Commun. 2, 135. https://doi.org/10.1186/s40478-014-0135-5.
Moulton, M.J., Barish, S., Ralhan, I., Chang, J., Goodman, L.D., Harland, J.G., Marcogliese, P.C., Johansson, J.O., Ioannou, M.S., Bellen, H.J., 2021. Neuronal ROS-induced glial lipid droplet formation is altered by loss of Alzheimer's disease-associated genes. Proc. Natl. Acad. Sci. Usa. 118, e2112095118. https://doi.org/10.1073/pnas.2112095118.
Mowry, F.E., Espejo-Porras, F., Jin, S., Quadri, Z., Wu, L., Bertolio, M., Jarvis, R., Reynolds, C., Alananzeh, R., Bieberich, E., Yang, Y., 2023. Chronic nSMase inhibition suppresses neuronal exosome spreading and sex-specifically attenuates amyloid pathology in APP knock-in Alzheimer's disease mice. Neurobiol. Dis. 184, 106213. https://doi.org/10.1016/j.nbd.2023.106213.
Nakano, A., 2022. The Golgi Apparatus and its Next-Door Neighbors. Front Cell Dev. Biol. 10, 884360. https://doi.org/10.3389/fcell.2022.884360.
Nalivaeva, N.N., Turner, A.J., 2013. The amyloid precursor protein: a biochemical enigma in brain development, function and disease. FEBS Lett. 587, 2046–2054. https://doi.org/10.1016/j.febslet.2013.05.010.
Neuman, S.D., Lee, A.R., Selegue, J.E., Cavanagh, A.T., Bashirullah, A., 2021. A novel function for Rab1 and Rab11 during secretory granule maturation. J. Cell Sci. 134, jcs259037. https://doi.org/10.1242/jcs.259037.
Ni, Y., Zhao, X., Bao, G., Zou, L., Teng, L., Wang, Z., Song, M., Xiong, J., Bai, Y., Pei, G., 2006. Activation of beta2-adrenergic receptor stimulates gamma-secretase activity and accelerates amyloid plaque formation. Nat. Med 12, 1390–1396. https://doi.org/10.1038/nm1485.
van Niel, G., Bergam, P., Di Cicco, A., Hurbain, I., Lo Cicero, A., Dingli, F., Palmulli, R., Fort, C., Potier, M.C., Schurgers, L.J., Loew, D., Levy, D., Raposo, G., 2015. Apolipoprotein E regulates amyloid formation within endosomes of pigment cells. Cell Rep. 13, 43–51. https://doi.org/10.1016/j.celrep.2015.08.057.
Nithianandam, V., Bukhari, H., Leventhal, M.J., Battaglia, R.A., Dong, X., Fraenkel, E., Feany, M.B., 2023. Integrative analysis reveals a conserved role for the amyloid precursor protein in proteostasis during aging. Nat. Commun. 14, 7034. https://doi.org/10.1038/s41467-023-42822-1.
Nusbaum, M.P., Blitz, D.M., Marder, E., 2017. Functional consequences of neuropeptide and small-molecule co-transmission. Nat. Rev. Neurosci. 18, 389–403. https://doi.org/10.1038/nrn.2017.56.
Odonchimed, S., Imamura, K., Inoue, H., 2026. Neurodegenerative disease and autophagy in iPSC-based models. Neurosci. Res 222, 104991. https://doi.org/10.1016/j.neures.2025.104991.
Oettinger, D., Yamamoto, A., 2025. Autophagy Dysfunction and Neurodegeneration: Where Does It Go Wrong? J. Mol. Biol. 437, 169219. https://doi.org/10.1016/j.jmb.2025.169219.
Rajendran, L., Honsho, M., Zahn, T.R., Keller, P., Geiger, K.D., Verkade, P., Simons, K., 2006. Alzheimer's disease beta-amyloid peptides are released in association with exosomes. Proc. Natl. Acad. Sci. Usa. 103, 11172–11177. https://doi.org/10.1073/pnas.0603838103.
Rawat, P., Sehar, U., Bisht, J., Selman, A., Culberson, J., Reddy, P.H., 2022. Phosphorylated Tau in Alzheimer's Disease and Other Tauopathies. Int J. Mol. Sci. 23, 12841. https://doi.org/10.3390/ijms232112841.
Redhai, S., Hellberg, J.E., Wainwright, M., Perera, S.W., Castellanos, F., Kroeger, B., Gandy, C., Leiblich, A., Corrigan, L., Hilton, T., Patel, B., Fan, S.J., Hamdy, F., Goberdhan, D.C., Wilson, C., 2016. Regulation of Dense-Core Granule Replenishment by Autocrine BMP Signalling in *Drosophila* Secondary Cells. PLoS Genet 12, e1006366. https://doi.org/10.1371/journal.pgen.1006366.
Reid, E., Connell, J., Edwards, T.L., Duley, S., Brown, S.E., Sanderson, C.M., 2005. The hereditary spastic paraplegia protein spastin interacts with the ESCRT-III complex-associated endosomal protein CHMP1B. Hum. Mol. Genet 14, 19–38. https://doi.org/10.1093/hmg/ddi003.
Roda, A.R., Serra-Mir, G., Montoliu-Gaya, L., Tiessler, L., Villegas, S., 2022. Amyloid-beta peptide and tau protein crosstalk in Alzheimer's disease. Neural Regen. Res 17, 1666–1674. https://doi.org/10.4103/1673-5374.332127.
Rolland, M., Powell, R., Jacquier-Sarlin, M., Boisseau, S., Reynaud-Dulaurier, R., Martinez-Hernandez, J., André, L., Borel, E., Buisson, A., Lanté, F., 2020. Effect of Aβ Oligomers on Neuronal APP Triggers a Vicious Cycle Leading to the Propagation of Synaptic Plasticity Alterations to Healthy Neurons. J. Neurosci. 40, 5161–5176. https://doi.org/10.1523/JNEUROSCI.2501-19.2020.
Sannerud, R., Esselens, C., Ejsmont, P., Mattera, R., Rochin, L., Tharkeshwar, A.K., De Baets, G., De Wever, V., Habets, R., Baert, V., Vermeire, W., Michiels, C., Groot, A.J., Wouters, R., Dillen, K., Vints, K., Baatsen, P., Munck, S., Derua, R., Waelkens, E., Basi, G.S., Mercken, M., Vooijs, M., Bollen, M., Schymkowitz, J., Rousseau, F., Bonifacino, J.S., Van Niel, G., De Selkoe, D.J., Hardy, J., 2016. The amyloid hypothesis of Alzheimer's disease at 25 years. EMBO Mol. Med 8, 595–608. https://doi.org/10.15252/emmm.201606210.
Sardar Sinha, M., Ansell-Schultz, A., Civitelli, L., Hildesjö, C., Larsson, M., Lannfelt, L., Ingelsson, M., Hallbeck, M., 2018. Alzheimer's disease pathology propagation by exosomes containing toxic amyloid-beta oligomers. Acta Neuropathol. 136, 41–56. https://doi.org/10.1007/s00401-018-1868-1.
Schulz, L., Ramirez, P., Lemieux, A., Gonzalez, E., Thomson, T., Frost, B., 2023. Tau-induced elevation of the activity-regulated cytoskeleton associated protein arc1 causally mediates neurodegeneration in the Adult *Drosophila* Brain. Neuroscience 518, 101–111. https://doi.org/10.1016/j.neuroscience.2022.04.017.
Schützmann, M.P., Hasecke, F., Bachmann, S., Zielinski, M., Hänsch, S., Schröder, G.F., Zempel, H., Hoyer, W., 2021. Endo-lysosomal Aβ concentration and pH trigger formation of Aβ oligomers that potently induce Tau missorting. Nat. Commun. 12, 4634. https://doi.org/10.1038/s41467-021-24900-4.
Selkoe, D.J., Hardy, J., 2016. The amyloid hypothesis of Alzheimer's disease at 25 years. EMBO Mol Med. 8 (6), 595–608. https://doi.org/10.15252/emmm.201606210.
Shearer, L.J., Petersen, N.O., 2019. Distribution and Co-localization of endosome markers in cells. Heliyon 5, e02375. https://doi.org/10.1016/j.heliyon.2019.e02375.
Singh, P.J., Verma, B., Wells, A., Mendes, C.C., Dunn, D., Chen, Y.N., Oh, J., Blincowe, L., Wainwright, S.M., Fischer, R., Fan, S.J., Harris, A.L., Goberdhan, D.C.I., Wilson, C., 2025. Amyloid-β disrupts APP-regulated protein aggregation and dissociation from recycling endosomal membranes. EMBO J. 44, 4443–4472. https://doi.org/10.1038/s44318-025-00497-y.
Stenmark, H., 2009. Rab GTPases as coordinators of vesicle traffic. Nat. Rev. Mol. Cell Biol. 10, 513–525. https://doi.org/10.1038/nrm2728.
Stockhammer, A., Adarska, P., Natalia, V., Heuhsen, A., Klemt, A., Bregu, G., Harel, S., Rodilla-Ramirez, C., Spalt, C., Özsoy, E., Leupold, P., Grindel, A., Fox, E., Mejedo, J. O., Zehtabian, A., Ewers, H., Puchkov, D., Haucke, V., Bottanelli, F., 2024. ARF1 compartments direct cargo flow via maturation into recycling endosomes. Nat. Cell Biol. 26, 1845–1859. https://doi.org/10.1038/s41556-024-01518-4.
Strooper, B., Annaert, W., 2016. Restricted Location of PSEN2/γ-Secretase Determines Substrate Specificity and Generates an Intracellular Aβ Pool. Cell 166, 193–208. https://doi.org/10.1016/j.cell.2016.05.020.
Sugawara, K., Shibasaki, T., Mizoguchi, A., Saito, T., Seino, S., 2009. Rab11 and its effector Rip11 participate in regulation of insulin granule exocytosis. Genes Cells 14, 445–456. https://doi.org/10.1111/j.1365-2443.2009.01285.x.
Sullivan, K.R., Ravens, A., Walker, A.C., Shepherd, J.D., 2025. "Arc - A viral vector of memory and synaptic plasticity". Curr. Opin. Neurobiol. 91, 102979. https://doi.org/10.1016/j.conb.2025.102979.
Szenci, G., Csizmadia, T., Juhász, G., 2023. The role of crinophagy in quality control of the regulated secretory pathway. J. Cell Sci. 136, jcs260741. https://doi.org/10.1242/jcs.260741.
Tampellini, D., Gouras, G.K., 2010. Synapses, synaptic activity and intraneuronal abeta in Alzheimer's disease. Front Aging Neurosci. 2, 13. https://doi.org/10.3389/fnagi.2010.00013.
Tan, J.Z.A., Fourriere, L., Wang, J., Perez, F., Boncompain, G., Gleeson, P.A., 2020. Distinct anterograde trafficking pathways of BACE1 and amyloid precursor protein

from the TGN and the regulation of amyloid-β production. Mol. Biol. Cell 31, 27–44. https://doi.org/10.1091/mbc.E19-09-0487.
Thomas, L.L., Highland, C.M., Fromme, J.C., 2021. Arf1 orchestrates Rab GTPase conversion at the trans-Golgi network. Mol. Biol. Cell 32, 1104–1120. https://doi.org/10.1091/mbc.E20-10-0664.
Tong, M.K., Thakur, A., Yang, T., Wong, S.K., Li, W.K., Lee, Y., 2024. Amyloid-β oligomer-induced neurotoxicity by exosomal interactions between neuron and microglia. Biochem Biophys. Res Commun. 727, 150312. https://doi.org/10.1016/j.bbrc.2024.150312.
Tsintzas, E., Niccoli, T., 2024. Using *Drosophila* amyloid toxicity models to study Alzheimer's disease. Ann. Hum. Genet 88, 349–363. https://doi.org/10.1111/ahg.12554.
Urwin, H., Ghazi-Noori, S., Collinge, J., Isaacs, A., 2009. The role of CHMP2B in frontotemporal dementia. Biochem Soc. Trans. 37 (Pt 1), 208–212. https://doi.org/10.1042/BST0370208.
Vaillant-Beuchot, L., Mary, A., Pardossi-Piquard, R., Bourgeois, A., Lauritzen, I., Eysert, F., Kinoshita, P.F., Cazareth, J., Badot, C., Fragaki, K., Bussiere, R., Martin, C., Mary, R., Bauer, C., Pagnotta, S., Paquis-Flucklinger, V., Buée-Scherrer, V., Buée, L., Lacas-Gervais, S., Checler, F., Chami, M., 2021. Accumulation of amyloid precursor protein C-terminal fragments triggers mitochondrial structure, function, and mitophagy defects in Alzheimer's disease models and human brains. Acta Neuropathol. 141, 39–65. https://doi.org/10.1007/s00401-020-02234-7.
Vale-Costa, S., Amorim, M.J., 2016. Recycling endosomes and viral infection. Viruses 8, 64. https://doi.org/10.3390/v8030064.
Vrancx, C., Annaert, W., 2025. Amyloid precursor protein carboxy-terminal fragments as catalyzers of endolysosomal dysfunction in Alzheimer's disease. Trends Neurosci. 48, 538–551. https://doi.org/10.1016/j.tins.2025.05.007.
Walsh, R.B., Dresselhaus, E.C., Becalska, A.N., Zunitch, M.J., Blanchette, C.R., Scalera, A. L., Lemos, T., Lee, S.M., Apiki, J., Wang, S., Isaac, B., Yeh, A., Koles, K., Rodal, A.A., 2021. Opposing functions for retromer and Rab11 in extracellular vesicle traffic at presynaptic terminals. J. Cell Biol. 220, e202012034. https://doi.org/10.1083/jcb.202012034.
Wang, J., Fourriere, L., Gleeson, P.A., 2024. Advances in the cell biology of the trafficking and processing of amyloid precursor protein: impact of familial Alzheimer's disease mutations. Biochem J. 481, 1297–1325. https://doi.org/10.1042/BCJ20240056.
Wang, L., Lin, G., Zuo, Z., Li, Y., Byeon, S.K., Pandey, A., Bellen, H.J., 2022. Neuronal activity induces glucosylceramide that is secreted via exosomes for lysosomal degradation in glia. Sci. Adv. 8, eabn3326. https://doi.org/10.1126/sciadv.abn3326.
Wang, X., Arpino, G., Mohseni, A., Bleck, C.K.E., Wu, L.G., 2025. Dense-core vesicles contain exosomes in secretory cells. Biophys. J. 124, 1747–1752. https://doi.org/10.1016/j.bpj.2025.01.003.
Weglinski, C., Jeans, A., 2023. Amyloid-β in Alzheimer's disease - front and centre after all? Neuron Signal 7, NS20220086. https://doi.org/10.1042/NS20220086.
Wells, A., Mendes, C.C., Castellanos, F., Mountain, P., Wright, T., Wainwright, S.M., Stefana, M.I., Harris, A.L., Goberdhan, D.C.I., Wilson, C., 2023. A Rab6 to Rab11 transition is required for dense-core granule and exosome biogenesis in *Drosophila* secondary cells. PLoS Genet 19, e1010979. https://doi.org/10.1371/journal.pgen.1010979.
Welz, T., Wellbourne-Wood, J., Kerkhoff, E., 2014. Orchestration of cell surface proteins by Rab11. Trends Cell Biol. 24, 407–415. https://doi.org/10.1016/j.tcb.2014.02.004.
Wilmes, S., Kümmel, D., 2023. Insights into the role of the membranes in Rab GTPase regulation. Curr. Opin. Cell Biol. 83, 102177. https://doi.org/10.1016/j.ceb.2023.102177.
Wu, J., Petralia, R.S., Kurushima, H., Patel, H., Jung, M.Y., Volk, L., Chowdhury, S., Shepherd, J.D., Dehoff, M., Li, Y., Kuhl, D., Huganir, R.L., Price, D.L., Scannevin, R., Troncoso, J.C., Wong, P.C., Worley, P.F., 2011. Arc/Arg3.1 regulates an endosomal pathway essential for activity-dependent β-amyloid generation. Cell 147, 615–628. https://doi.org/10.1016/j.cell.2011.09.036.
Yeapuri, P., Machhi, J., Foster, E.G., Kadry, R., Bhattarai, S., Lu, Y., Sil, S., Sapkota, R., Srivastava, S., Kumar, M., Ikezu, T., Poluektova, L.Y., Gendelman, H.E., Mosley, R.L., 2025. Amyloid precursor protein and presenilin-1 knock-in immunodeficient mice exhibit intraneuronal Aβ pathology, microgliosis, and extensive neuronal loss. Alzheimers Dement 21, e70084. https://doi.org/10.1002/alz.70084.
Zhang, Y., Kunii, M., Taniguchi, M., Yoshimura, S.I., Harada, A., 2024. Rab6-Mediated Polarized Transport of Synaptic Vesicle Precursors Is Essential for the Establishment of Neuronal Polarity and Brain Formation. J. Neurosci. 44, e2334232024. https://doi.org/10.1523/JNEUROSCI.2334-23.2024.
Zhou, Y., Liu, Z., Zhang, S., Zhuang, R., Liu, H., Liu, X., Qiu, X., Zhang, M., Zheng, Y., Li, L., Hong, W., Wang, T., 2020. RILP Restricts Insulin Secretion Through Mediating Lysosomal Degradation of Proinsulin. Diabetes 69, 67–82. https://doi.org/10.2337/db19-0086.
Zhuang, L., Li, C., Peng, F., Xue, E., Li, W., Sun, X., Chen, P., Zhou, Q., Xue, L., 2023. Depletion of ESCRT ameliorates APP-induced AD-like symptoms in *Drosophila*. J. Cell Physiol. 238, 1567–1579. https://doi.org/10.1002/jcp.31035.

Glossary

Aβ-fibrils: insoluble aggregates of many Aβ-monomers forming fibrils, which can contribute to amyloid plaques
Aβ-oligomers: soluble aggregates of multiple Aβ-monomers
Amyloid plaques: extracellular deposits containing Aβ-fibrils, but also extracellular vesicles and other proteins
APP (Amyloid Precursor Protein): single-pass transmembrane protein, which can be cleaved to form neurotoxic Aβ and APP C-terminal fragments (Fig. 1)
Autophagy: multifaceted cellular process employed to degrade and recycle intracellular compartments and cytosol, typically by enveloping material in a double-membrane prior to lysosomal fusion. Some autophagic regulators also control specific forms of secretion (secretory autophagy) and ILV formation.
DCG (dense-core granule): intra-compartmental aggregate or condensate of proteins destined for secretion, which normally dissipates when the compartment fuses with the plasma membrane
Exosomes: extracellular vesicles formed inside endosomal MVBs
Familial AD: rare forms of genetically inherited AD in which mutations in APP/Aβ or tau for example typically ensure that affected individuals suffer from early-onset AD
ILVs (intraluminal vesicles): vesicles primarily found inside compartments with endosomal identity, usually formed by inward budding of the limiting membrane
LELs (late endosomes and lysosomes): compartments of the degradative endosomal system; late endosomes are the long-established (but not exclusive) origin of exosomes
MVBs (multivesicular bodies): intracellular membrane-bound compartments containing intraluminal vesicles, typically endosomal in origin
Neurofibrillary tangles: intracellular pathological aggregates of hyper-phosphorylated tau protein
Regulated secretion: a form of secretion in which the production and release of secretory compartments is controlled, typically by hormones, other extracellular signals or membrane depolarisation; this contrasts with constitutive secretion where secretion is continuous, primarily determined by the rate of new secretory compartment formation at the TGN
Secondary cells (SCs): prostate-like secretory cells of the male accessory gland in the fruit fly, *Drosophila melanogaster*, containing giant secretory compartments and lysosomes
Secretory granules: another term for DCGs
Secretory vesicles: a term used to describe regulated secretory compartments, which are distinct from the ILVs that may be present inside them and from vesicles that traffic material between different secretory and endosomal compartments
Sporadic AD: the common form of late-onset AD caused by a combination of genetic and environmental factors, in which many features of the pathology are shared with familial AD
Trans-Golgi network: the secretory exit site from the Golgi, where different cargos are sorted into specific compartments destined for constitutive or regulated secretion, or into compartments involved in other cellular functions, eg. LELs
Tau: microtubule binding protein associated with neurofibrillary tangle formation and AD